Comparison of an Intermittent vs. Continuous Walking Program in Persons with Multiple Sclerosis Using the 6 Minute Walk Test: A Randomized Crossover Pilot Study

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Comparison of an Intermittent vs. Continuous Walking Program in Persons with Multiple Sclerosis Using the 6 Minute Walk Test

A Randomized Crossover Pilot Study

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A capstone project submitted to the Graduate Faculty in Physical Therapy in partial fulfillment of the requirements for the degree of Doctor of Physical Therapy, The City University of New York

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ABSTRACT

COMPARISON OF AN INTERMITTENT VS. CONTINUOUS WALKING PROGRAM IN PERSONS WITH MULTIPLE SCLEROSIS USING THE 6 MINUTE WALK TEST: A RANDOMIZED CROSSOVER PILOT STUDY

By

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Background: Difficulty with gait is one of the most common complaints of persons with MS (pwMS) and can be due to many causes, including neurogenic fatigue. Neurogenic fatigue is one of the most common MS symptoms, and can prevent pwMS from walking longer distances, thus limiting their ability to improve gait endurance. Intermittent walking, a technique where persons take breaks during walking rather than walking continuously, may allow for pwMS to walk longer distances due to less accrual of fatigue.

Objectives: The purpose of this pilot study was to examine whether a program of intermittent walking will result in a greater improvement in gait endurance in pwMS than a continuous walking program.

Methods: A randomized crossover design was used. Subjects were randomized into intermittent (INT) and continuous (CONT) groups. All subjects performed a baseline 6-minute walk test (6MWT), following which they performed a training regime of eight 6-minute walks over a 4-week period, followed by a 6MWT posttest. Subjects in the INT group trained with three 2-minute walks interspersed with 2 minute seated rests, while the CONT group trained 6 minutes continuously. Subjects then underwent a 4-week detraining period, followed by another 4-week walking period where they performed whatever type of training they did not perform.
originally, with 6MWTs performed before and after the 8 training bouts. To determine whether
the subjects found one type of training more fatiguing than the other, a Visual Analog Fatigue
Scale (VAFS) was used to measure subjective perception of fatigue for both walking conditions.

**Results:** 9 subjects (6 female, 3 male, EDSS 3.39) completed both training conditions.
Intermittent training resulted in a significant ($F (1,8) = 9.634, p < .015.$) improvement in 6MWT
(143.01’) relative to continuous training, which resulted in a decrease of 59.2’. Subjective
perceptions of fatigue while walking were not significantly different for the two walking
conditions.

**Conclusions:** Despite the small sample size, intermittent gait training was clearly superior to
continuous gait training in improving 6MWT performance. This suggests that gait endurance in
pwMS may be better improved with gait training that emphasizes intermittent rests as opposed to
walking continuously.
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**INTRODUCTION**

Multiple Sclerosis (MS) is a chronic degenerative inflammatory disease of the central nervous system (CNS), characterized by a loss in functional mobility (Hemmett, Holmes, Barnes, and Russel, 2004). Persons with MS (pwMS) can experience symptoms such as fatigue, spasticity, muscle weakness, and sensory disturbances which can lead to difficulties with balance, ambulation, and activities of daily living (ADL).

Walking, in particular, can be affected due to many factors, including but not limited to spasticity, poor motor control, and fatigue. Walking ability is one of the greatest concerns of pwMS and as such remains of high interest among researchers and clinicians (Heesen et al., 2008). Research shows that ambulation training improves walking endurance in pwMS (Dettmers, Ruchay-Plössl, Gütler & Vieten 2009); therefore, to maintain walking endurance ability, effective ambulation training must be performed. Neurogenic fatigue (NF) is often a primary limiting factor for ambulation training within this population. Fatigue prevents a pwMS from performing a high volume of work needed to generate improvements in fitness and resulting quality of life (QOL), therefore, a gait training program that limits fatigue while allowing for a sufficient volume of work to be performed may produce greater ambulation gains. Intermittent training (IT), an exercise program where rest periods are integrated into the exercise program prior to onset of fatigue, may offer a means of doing this, as research shows that intermittent training improves exercise outcomes in healthy, disabled, and MS populations (Clapp et al., 1999; Karpatkin, 2006; Karpatkin & Rzetelny, 2012; Karpatkin et al., 2012; Sabapathy et al., 2004; Weltman et al., 2008).

The purpose of this study is to examine whether an intermittent walking program, for pwMS, will result in better endurance and greater improvement in distance walked than a continuous walking program. It is hypothesized that intermittent walking will result in greater
improvements than continuous walking in pwMS. If this hypothesis is correct, pwMS will be able to perform a greater amount of gait training and therefore recognize greater improvements in gait, fitness, and overall QOL.

FATIGUE

Fatigue as a symptom

Persons with MS are faced with both short and a long term challenges. These can be compounded by motor and psychological effects, all which are related to neurogenic fatigue. The MS Council of Clinical Practice guidelines (1998) defines fatigue as: “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” (p. 2). According to the MS Council, “fatigue is now recognized as the most common symptom of MS” (p. 1). Seventy-five to ninety-five percent of those afflicted name fatigue as a symptom, with 50-60% considering fatigue the worst problem they face (MS Council, 1998). Similarly, Iriarte, Subira, and De Castro (2000) evaluated 155 pwMS using the Fatigue Descriptive Scale (FDS) along with the Fatigue Severity Scale (FSS) and found that approximately 50% of participants reported physical limitation due to fatigue. In their retrospective medical record study of 16,976 pwMS from the Thomson Reuters MarketScan Databases, Berger, Pocoski, Preblick, and Boklage (2013) found that 28.9% of patients were diagnosed with fatigue three years prior to their MS diagnosis and 40% complained of fatigue as one of the earliest symptoms. This demonstrates the prevalence of MS fatigue and how it could be one of many indicative factors for the disease.

Types of fatigue

Fatigue, being a subjective feeling of an objective response, is very difficult to study though many researchers have explored it. MS fatigue has many dimensions and therefore
certain divisions, or subcategories, must be established. Paty and Ebers (1998) distinguished two subcategories of MS fatigue: lassitude and motor fatigue. Lassitude is defined as a generalized feeling of exhaustion, whereas motor fatigue occurs with repeated muscle contractions or continued motor activity (Paty & Ebers, 1998). A global fatigue such as lassitude may present as an overall feeling of tiredness or sleepiness that is not quantifiable objectively other than through subjective fatigue scales such as the Visual Analogue Scale of Fatigue (VASF) (Schwid, Covington, Segal, & Goodman, 2002). Motor fatigue, however, can be objectively measured by comparing a muscle or muscle group’s force output before and after a fatiguing activity (Schwid et al., 2002). Certain movement compensations may occur if someone is experiencing motor fatigue. For example, hip external rotation may occur with hip flexion during gait indicating a fatigue of the iliopsoas and compensation by the sartorius. Lassitude and motor fatigue can further be broken down based on the context in which a person experiences them. Iriarte et al. (2000) found that among participants in their survey on MS fatigue, 72% experienced fatigue when exercising (“fatigability”), 22% reported fatigue as “asthenia” (fatigue when resting), and 5.9% reported fatigue as “the worsening of other symptoms” (pg. 125). Another method of breaking down MS fatigue is into primary and secondary fatigue. Primary, or neurogenic fatigue, is caused by an underlying cellular pathology; whereas secondary fatigue results from the subsequent muscle disuse atrophy and deconditioning that occurs when a person is unable to maintain a healthy level of fitness. When primary fatigue prevents a pwMS from achieving a high enough volume of exercise, secondary fatigue becomes more of a problem. Identifying the type of fatigue and when it occurs can assist in generation of a proper plan of care and management.
Neurological causes of primary fatigue

It is important to recognize MS as a neurological disease, and therefore the mechanism of primary fatigue as a symptom must be studied in the context of the nervous system. Krupp (2004) analyzed existing research focusing on the diagnosis and management of MS related fatigue, and found the impairment it has on physical activity is directly connected to the degenerative pathophysiology of MS, including: “immune deregulation, inflammation, neuronal dysfunction, and demyelination” (pg. 8). Although the pathophysiology behind MS fatigue is not well understood, several theories exist. Hemmer, Cepok, Nessler, and Sommer (2002) developed the neuromodulation theory, which states that fatigue may be related to an autoimmune dysfunction where increased leukocyte activity causes an influx of proinflammatory cytokines, which in turn worsen inflammation symptoms. Chao et al. (1991) and Buchwald, Wener, Pearlman and Kith (1997) found that proinflammatory cytokines levels are typically elevated in MS lesions and have been shown to cause fatigue and drowsiness when administered exogenously. Further supporting the neuromodulation theory, Vgontzas et al. (2000) and Dreisbach, Hendrickson, Beezhold, Riesenber, and Sklar (1998) noted altered levels of peripheral cytokines in other conditions associated with fatigue.

Current research supports compromised cortical functioning as a contributing factor of MS fatigue. Yusuf and Koski (2013) performed a literature review investigating altered excitatory or inhibitory cortical activity and its possible effect on fatigue in pwMS. They were unable to determine any correlations with perceived levels of fatigue; however, they did find support for a central fatigue theory. The literature review included 40 published studies involving transcranial magnetic stimulation (TMS) performed on pwMS and healthy controls as a means of measuring neural conductivity. Two categories of interest involved corticospinal neural excitability and intracortical inhibition and facilitation. Some of the studies reviewed
produced results within both of these categories. The studies involving corticospinal neural excitability encompassed 35 of the 40 papers reviewed. Fifty percent of those studies looked at motor thresholds (the lowest intensity needed for a motor response) and found pwMS had higher thresholds than healthy controls. Additionally, 68% found smaller motor evoked potentials (MEPs) in pwMS. Both findings indicate possible reduced neural membrane excitability, a decrease in the number of cortical neurons, axonal loss, a blockage within the conduction path, and/or diminished strength of corticospinals projections; all of which can result in diminished signal conduction leading to a decrease in motor response. Eighty-five percent of pwMS had increased central motor conduction time (CMCT); meaning signals took longer to travel from the motor cortex to the spinal cord which could be due to axonal demyelination, a loss of large neural fibers and/or slow summation of excitatory potentials. Three studies looked at, but did not find a correlation between, self-perceived fatigue and motor threshold levels, MEPs, or CMCT.

Within the review by Yusuf and Koski (2013), only four studies investigated intracortical inhibition, specifically short interval intracortical inhibition (SICI), which decreases MEP amplitude therefore having an inhibitory effect on neural signals. Seventy-five percent of these studies reported a reduction in this natural inhibitory effect occurring in pwMS as compared to controls, but only one found a correlation between those reporting high levels of fatigue and those who also had reduced short interval intracortical inhibition. Currently, reduction of SICI remains a possible contributor to MS fatigue but requires further investigation. This literature review does not specifically address exercise related fatigue other than to conclude that current literature does not fully demonstrate a link between it and altered cortical excitability.
Additionally, the study does not address patients who have lesions within their spinal cord, as opposed to cortical lesions, nor those who demonstrate fatigue with activity.

Chaudhuri and Behan (2000) similarly discovered that physical or cognitive impairments may be caused by cerebral hypometabolism or signaling defects, both of which affect information processing. The authors suggest that demyelination and axonal loss in motor nerve tracts running from the cortex to the spinal cord result in decreased motor function. Damage to these corticospinal tracts, therefore, may lead to impaired activation of alpha motor neurons in the spinal cord and lower a person’s ability to move their extremities (Rice, Volmer, & Bigland-Ritchie, 1992). Sandroni, Cameron, and Starr (1992) found a delay between the recognition of a stimulus and the subsequent activation of a motor response while studying EMG activity during auditory memory tasks. This delay suggests conduction disturbances exist along the signal pathways. Roelcke et al. (1997) used functional MRIs (fMRIs) in pwMS who reported fatigue and noticed a decrease in metabolic activity in parts of the brain required for motor planning and execution. Specifically, there was a decrease in activation of the thalamus, prefrontal cortex, and the basal ganglia which correlated with increased scores on fatigue scales.

Sheena, Murray, Rothwell, Miller, and Thompson (1997) studied motor fatigue by measuring the decline in strength of the right adductor pollicis muscle during a maximal contraction held for 45 seconds in 21 pwMS and 19 healthy subjects. The MS group’s results showed their strength to be significantly limited by fatigue. Those with MS demonstrated a substantial decline in rate of force, a significant decline in central activation, and a decrease in the mean stimulated twitch force, indicating that such fatigue is predominantly caused by a failure of “central motor drive” to alpha motor fibers exiting the spinal cord (p. 309). The aforementioned studies conducted by Chaudhuri and Behan (2000), Sandroni et al. (1992),
Roelcke et al. (1997), and Sheena et al. (1997) strongly suggest MS fatigue may result from interference in communication throughout the cerebral cortex and between the cortex and spinal cord.

**Environmental effects on fatigue**

Heat has been shown to exacerbate MS fatigue which can lead to a reduction in exercise endurance. Bakshi (2003) in a literature review focusing on the diagnosis, impact, and management of MS, found adverse effects on exercising within that population. In particular, the increased body heat generated with exercise exacerbated the existing disabilities resulting from demyelination and impaired nerve conduction. A rise of internal body temperature can create both lassitude and motor fatigue due to transmission disruptions in nerve signal conduction that decrease a person’s ability to attain a certain level of muscle contraction. In addition, cognitive disruptions occurred after exercise, which are likely due to a central metabolic compromise caused by the rise in temperature. According to Bakshi, this common complaint of MS heat sensitivity leads to physiological fatigue, contributes to an aversion to exercising, and subsequently to disuse atrophy and cardiovascular detraining.

Further demonstrating the damaging effect heat sensitivity can have on subjective symptoms in pwMS, Skjerbæk, et al. (2012) compared changes in VASF measures of spasticity, fatigue, balance, pain, and strength after 30 minutes of endurance training and separately after 30 minutes of resistance training. Measurements were recorded before, immediately after, and one hour later for 19 subjects that participated. Exercise intensity was 60% of the individual subject’s VO2-peak for endurance exercise and equal to a 12 Rep Max for resistance exercise. Internal body temperature, along with symptom intensity and total number of symptoms, increased after both forms of exercise but was significantly higher after endurance training. The
study focused on the overall intensity of subjective symptoms using a VASF and so it is difficult to differentiate the effect an increase in body temperature had on fatigue alone. Most interestingly, the increase in symptom intensity and number were still present one hour later only in the MS group indicating a possible disease related disruption in thermoregulation.

In a review of current literature, Davis, Wilson, White, and Frohman, (2010) investigated general heat sensitivity and heat induced fatigue in pwMS. They found that the decreased conduction occurring in demyelinated nerve fibers is exacerbated with even slight increases in body temperature. It was documented that with a 0.8°C increase in core body temperature, pwMS showed a decreased central motor conduction time along with decreased central excitability. This combination has the potential to create a nerve block which could present like motor fatigue.

MS lesions can occur anywhere in the CNS, including areas responsible for thermoregulation. If this were to occur, pwMS would be unable to auto-regulate an increase in internal body temperature, which could bring on heat related fatigue as noted in Skjerbæk et al. (2012). The findings of Davis et al. (2010) support a literature review by Guthrie and Dewey (1995), which summarized experiments using hot bath immersion and small heated rooms that induced profound weakness and symptom exacerbation in 75-100% of MS subjects. Based on information from Skjerbæk et al. and Davis et al., this reported weakness was likely due to fatigue from decreased signal conduction brought on by heat in already compromised nerves.

**Subjectivity of MS fatigue**

Due to its subjectivity, MS fatigue does not always correlate to physical limitation. Feys et al. (2011) examined the effect of time of day on ambulation and corresponding subjective feelings of fatigue in 102 pwMS having EDSS scores less than 6.5 and similar self-perceived
fatigue levels. The 6 Minute Walk Test (6MWT) and the 10 Meter Walk Test were used to measure walking capacity in the morning, at noon, and in the afternoon during the course of one day. Subjects were instructed to walk at their normal pace and at their fastest speed. Subjects' fatigue worsened throughout the day as indicated by the Rochester Fatigue Diary (RFD); however, neither the mildly disabled group (EDSS 1.5-4.0) nor the moderately disabled group (EDSS 4.5-6.5) showed any change in walking capacity.

Morris et al. (2002) measured changes in walking patterns and self-perceived fatigue in 14 pwMS and compared those values to 14 control subjects of same age throughout a single day. Walking speed, stride length, cadence, and percentage of double support during the gait cycle were measured at 10am and again at 3pm. Subjects included had mild to moderate MS with a mean EDSS score of 3.8. Subjects reported dysfunctions such as muscle weakness, instability, a lack of coordination, and spasticity. Persons with MS walked slower, with a shorter stride length, and had significantly more variability in gait performance than the control subjects. Using an eleven-point scale, MS subjects rated their fatigue as increasing from the morning to the afternoon; however, footstep patterns did not vary in either group during the day. Both this study and that of Feys et al. (2011) indicate that perceived fatigue does not necessarily correlate to the motoric function of gait. There may be a deeper, physiological change occurring within the body that may only be addressed through physical therapy interventions.

**Functional limitations due to MS fatigue**

One of the clinically significant problems with MS fatigue is its negative effect on balance and gait, with both primary and secondary fatigue implicated as possible causative factors. Studies by Jackson and Bigelow (2013), Emmerik, Remelius, Johnson, Chung, and Kent-Braun (2010), and Hebert and Corboy (2013) assessed the effects of fatigue on balance in
pwMS. Significant findings within these studies suggest a correlation between higher levels of fatigue and increased difficulty with balance and postural control, leading to an increased falls risk. Jackson and Bigelow (2013) found in their 15 subject study that at mid-day and after a fatiguing 6 minute walk, participants reported higher subjective fatigue on a VASF and demonstrated difficulty with static and dynamic balance tasks as well as general postural control. Participants were diagnosed with either Relapsing Remitting MS (RRMS) or Secondary Progressive MS (SPMS) and were tested on two separate occasions under two different conditions: rested (morning) and fatigued (afternoon). Data collection consisted of two trials where the individual’s balance was measured using computerized static posturography with variations of eyes opened, eyes closed, on a firm surface, and on a foam surface. Various kinetic and kinematic measures were utilized to assess subjects’ posture, including: center of pressure, anterior-posterior (AP) and medial-lateral (ML) sway, sway velocity, and limits of stability. The Mini-Best and Dynamic Gait Index (DGI) were used to assess falls risk. As expected, subjects reported significantly higher fatigue on the VASF in the afternoon vs morning sessions. When fatigued, subjects demonstrated an increase in ML sway when standing with eyes closed on a firm surface; an increase in AP sway and mean velocity with eyes opened on a foam surface; and significantly lower scores on both DGI and Mini-Best, indicating a higher potential for falls.

Jackson and Bigelow (2013) corroborated findings from Emmerik et al. (2010) who investigated the impact of MS fatigue on postural control during static standing and with movements involving leaning and reaching. The study compared a non-MS control group to 12 females diagnosed with MS for an average of 15 years. FSS and VASF scores measured fatigue and subjects’ postural control was measured using 36 retro-reflective markers on bony landmarks while subjects stood with both feet on two separate force plates. Researchers recorded data with
subjects standing quietly with their eyes open and closed and then challenged them by having them reach forward, backward, and to each side with eyes open, and again with the lights off. Compared to the control group, pwMS showed greater postural sway during quiet standing and smaller shifts of their center of pressure during leaning and reaching challenges, which could indicate a fear of movement. When comparing fatigue vs non-fatigued conditions in pwMS, no significant difference existed in static standing. However, with reaching and leaning challenges, fatigued pwMS moved less and therefore had smaller centers of pressure sway. This demonstrates that postural control is affected by fatigue and that pwMS may adapt and compensate their movements as they fatigue. This was especially noted in posterior postural control during a backward lean indicating a possible falls risk with backward movements. One limitation of this study is the moderate VASF scores. It was suggested that with higher levels of fatigue, postural difficulties may be noted in static standing as well as in leaning and reaching tasks.

Hebert and Corboy (2013) further investigated the effect of fatigue on balance by examining sensory integration within the CNS. Computerized dynamic posturography (SMART Balance Master system) was used to administer a sensory organization test (SOT) on 17 subjects with MS. Fatigue was measured using the Modified Fatigue Impact Scale. Results indicated higher fatigue levels correlated to lower balance scores with statistical significance. In addition, the researchers found that fatigue accurately predicted balance levels, and the most significant effects of fatigue on balance were found for those with cerebellar and brainstem dysfunction.

**Impact of MS fatigue on activity level**

MS fatigue, both primary and secondary, contributes to an inability to perform activities of daily living. The general malaise and lack of energy along with significant decreases in
strength during continuous activity are the most limiting impairments, but fatigue can also manifest as a lack of motivation. A lack of desire to exercise, coupled with a physical inability for sustained exercise, can cause a person with MS to enter into a vicious cycle whereby residual muscle atrophy and deconditioning leads to further activity related fatigue. The effect on a person's functional daily activities makes fatigue largely responsible for unemployment among individuals with MS (MS Council, 1998).

Surveys collected by Vercoulen et al. (1996) and Schreurs, Ridder, and De Bensing (2002) correlate fatigue with decreased activity levels. Vercoulen et al. compared fatigue in 50 pwMS to 51 persons with chronic fatigue syndrome (CFS) and 53 healthy subjects. Individuals with MS had similar subjective FSS values to those with CFS, which were significantly greater than those of the healthy individuals. Both MS and CFS groups reported a substantially lower activity level than the healthy group, demonstrating the inverse relationship between fatigue and activity level. Schreurs et al. collected Multidimensional Fatigue Inventory (MFI) questionnaire data from 98 pwMS and found supporting evidence of fatigue limiting physical activity. Subjects completed the questionnaire at the commencement of the study and once again after a year. Physical fatigue was closely linked with reduced activity, which worsened over the year along with mental fatigue and activity level. In addition, a high number of those who listed physical fatigue on the questionnaire at the start of the study reported physical disabilities at the conclusion of the study, indicating fatigue as a possible precursor to disability.

Similarly, a 2011 mail-in survey of 635 pwMS, which included the Neurological Fatigue Index for MS Summary Scale and the Multiple Sclerosis Impact Scale, indicated a direct relationship between fatigue and functional limitation (Mills & Young, 2011). Individuals that reported a higher fatigue level also reported a decrease in functional ambulation. In this survey,
participants with a progressive form of the disease exhibited a higher severity of fatigue. Most interestingly, fatigue was worse in patients with decreased ambulatory ability, further displaying the link between inactivity and increased secondary fatigue.

**Secondary fatigue**

Fatigue in MS can both be the cause of and result from physical impairment that further limits one’s ability to exercise. MS fatigue prevents individuals from completing a high enough volume of exercise to impose overload on their muscles. Muscles within the body respond to imposed demands typically by increasing the size of individual fibers leading to a larger cross sectional area (Hernandez and Kravitz, n.d.). This is known as hypertrophy. Additionally, with such demands, muscles become more efficient in oxygen uptake and in their ability to function (Hernandez and Kravitz, n.d.). If an individual is unable to exercise a sufficient amount, muscles will atrophy and decrease in cross sectional area, force output, and efficiency, leading to secondary fatigue. This deconditioning that occurs with low activity or inactivity will result in decreased endurance and further fatigue (both lassitude and motor fatigue). This suggests that a lack of walking endurance may have more to do with muscle disuse atrophy and deconditioning than by previously discussed CNS causes. If indeed the case, it implies that MS fatigue, in part, can and should be treated with exercise.

**EXERCISE**

The use of exercise to improve function in MS is well established. Petajan et al. (1996) studied the effects of a 15 week aerobic training program on fitness and QOL in pwMS. Fifty four subjects with MS were randomly assigned to one of two groups: exercise or non-exercise. The exercise group participated in a 40 minute exercise program consisting of combined upper and lower extremity ergometer exercise performed three times weekly for 15 weeks. Physical
fitness level was measured using maximum oxygen consumption (VO2 max), isometric strength, body composition, and blood lipids values. Quality of life measures included Profile of Mood States (POMS), Sickness Impact Profile (SIP), and the FSS. The exercise group showed a significant increase in VO2 max and upper and lower extremity strength, with significant decreases in skinfolds, triglycerides, and very low density lipoproteins (VLDL). In addition, the exercise group demonstrated significantly reduced levels of depression at weeks five and ten, with decreased fatigue at week ten. All components of QOL measures increased. SIP values improved, including total SIP score, social interaction, emotional behavior, and recreation and past times. Fatigue, as measured by the FSS, did not change, indicating that exercise did not result in an exacerbation of fatigue-related symptoms. These results show that exercise training can improve both physical fitness levels and QOL in pwMS.

Kileff and Ashburn (2003) examined the effects of aerobic exercise on eight female subjects between the ages of 33-61 having moderate MS. The participants cycled for 30 minutes twice a week for 12 weeks at their maximum level of exertion. Subjects improved in muscle strength and cardiorespiratory function by the end of the 12 week period, as measured by the Guy's Neurological Disability Scale (GNDS), the Gullick, the Functional Reach Test, the 10 Meter Walk Test, and the 6MWT. In addition, subjects increased their distance walked on the 6MWT indicating an increase in walking endurance. Overall, the aerobic training contributed to the improvement in mobility and ability to perform daily functional activities.

Romberg et al. (2004) examined the effects of a six month exercise program involving endurance and strength training in patients with mild to moderate MS. Ninety-one subjects between the ages of 30-35 were randomized into a control group and an experimental group. The control group did not participate in any intervention. The experimental group performed
aerobic exercise in the form of aquatic training and resistance exercise using resistance bands for a period of 26 weeks. Subjects exercised in an inpatient rehabilitation setting during the first three weeks. The remaining 23 weeks were performed in an outpatient setting. Measurements were collected at the beginning of the treatment and again after six months. The primary outcome, walking speed, was measured using the 7.62 Meter Walk Test and the 500 Meter Walk Test. Additional tests were used to measure lower extremity strength, upper extremity endurance, dexterity, static balance, and peak oxygen uptakes. The experimental group increased in walking speed and knee flexion strength as compared to the control group. The dynamic weight lifting test also showed an increase in upper extremity strength.

White et al. (2004) examined functional capacity of the knee and ankle in pwMS. Eight subjects between the ages of 25-55 participated in an eight week exercise program in which they performed knee flexion, knee extension, plantar flexion, and dorsiflexion resistance training exercises two times a week. Muscle strength was measured using an isokinetic dynamometer before and during the last two weeks of training. Walking speed was measured using the 25 Foot Walk Test before and after training. Subjects experienced a significant increase in stepping performance, knee extension, and plantar flexion strength as well as an increase in the cross sectional area of the hamstrings and quadriceps. A self-reported fatigue scale showed a decrease in perceived fatigue after the training program. Although walking speed did not increase significantly, the average step rate increased significantly by 8.7% confirming Romberg et al. (2004)’s findings that an increase in gait cadence is achievable through lower extremity strength training.

Tarckci, et al. (2013) performed a randomized single-blind controlled study to investigate the effectiveness of a 12 week group exercise training program on balance, functional capacity,
spasticity, fatigue, and QOL in pwMS. Subjects in the experimental group performed group exercise training consisting of a wide range of exercises performed in groups of six to seven persons with similar EDSS scores. Three 60 minute exercise sessions were held per week for 12 weeks (36 sessions), with the control group having no intervention. Primary outcome measures included the Berg Balance Scale (BBS), 10 Meter Walk Test, and 10 Step Climbing Test. Ninety-nine subjects completed the study, with results showing improvement in all outcome measures for the exercise group. The control group demonstrated poorer performance in the BBS and 10 Meter Walk Test, and a decrease in FSS scores indicating lower levels of fatigue. The study suggests that exercise training is effective to improve balance, functional status, spasticity, fatigue, and QOL for people with MS.

GAIT TRAINING & THE 6 MINUTE WALK TEST

Gait interventions have been extensively studied in pwMS, and many studies have shown that gait training can significantly improve walking endurance within that population. Dettmers, Ruchay-Plössl, Gütler, and Vieten (2009) explored the effects of an integrated low-level gait endurance program on walking performance in 30 subjects with MS. The interventions lasted 45 minutes and were performed at an inpatient rehabilitation center three times weekly, for three weeks. The experimental group performed mild strength training, and then walked around the rehabilitation facility while picking up objects or throwing balls at cans. The control intervention consisted of stretching, as well as sensory, balance, and coordination exercises, but no walking. After three weeks, the subjects receiving the intervention improved their maximal walking distance by 66% (as measured on a treadmill), whereas the control group did not improve at all. To calculate walking distance, patients walked on the treadmill at a predetermined comfortable pace until they felt they needed a break. At this point they stopped,
and the distance they walked was recorded. The study concluded that endurance training has a significant effect on maximal walking distance. In addition, given that the endurance exercise in this study involved walking, it can also be inferred that gait training in particular, could improve walking ability in pwMS.

Newman et al. (2007) examined the effects of treadmill training on maximum walking distance and speed in pwMS. After completing a four-week aerobic treadmill training program, subjects with mild to moderate MS experienced a reduction in resting metabolism, decreased times on the 10 Meter Walk Test, increased distance on the 2 Minute Walk Test, increased walking speed on the treadmill, a decrease in walking effort (measured by oxygen consumption), and a closer to normal temporo-spatial gait pattern during over ground walking (measured with a GAITRite pressure sensitive mat during the first half of the 2 Minute Walk Test).

In a pilot study, Gervasoni, Cattaneo, and Jonsdottir (2014) examined the effects of treadmill training on rate of perceived exertion (RPE), heart rate (HR), and fatigue (FSS) in 30 subjects with MS. The experimental group performed 12 sessions of treadmill walking for 15 minutes over a two week period. Subjects were told to walk at an RPE of 11 or 12. The slope and speed of the treadmill were adjusted during sessions, which the authors explained was to encourage adaptation of gait mechanics. After 12 sessions, the experimental group experienced a significant decrease in RPE while walking on a treadmill, and a decreased change in HR after walking on a treadmill, whereas the control group, which received standard therapy, did not. These results show that treadmill training helps to decrease walking effort (lower RPE) and increase cardiovascular efficiency (lower HR) in pwMS.

Neither Newman et al. (2007), Dettmers et al. (2009), nor Gervasoni et al. (2014) observed significant differences in subjective feelings of fatigue after their walking interventions.
In addition, Dettmers et al. found a decrease in measures of fatigue in the control group, which did not undergo the walking intervention. This may have been due to the taxing nature of the interventions, which promoted fatigue despite improving the physical fitness of the subjects. Walking as a training protocol, therefore, has shown to have positive effects on walking ability and overall fitness, but it also may increase fatigue.

Olgiati, Jacquet, and di Prampero (1986) found that a higher energy cost of walking could contribute to the fatigue and dyspnea experienced by pwMS during ambulation. The effects of low-speed treadmill walking on pulmonary function were examined in 24 subjects with MS. During treadmill walking, heart rate, minute ventilation, and oxygen consumption were all elevated by 37-119% compared to the control group, indicating a higher energy cost of walking. A follow up study by Olgiati, Burgunder, and Mumenthaler (1988) investigated the source of the fatigue pwMS experience when walking. Thirty-three pwMS, all with lower extremity involvement, were assessed for spasticity, weakness, and ataxia of the LEs and trunk. Step climbing was used to measure lower extremity weakness. Flexion-extension time at the knee joint was used to assess spasticity. Circle drawing, where the subject draws a circle on the floor with a pencil attached to their foot, was used to assess lower extremity movement. A sitting-up test was used to determine trunk strength. Oxygen consumption was measured while subjects walked on a treadmill, and walking speed was measured using the 10 Meter Walk Test. The results confirmed previous findings that pwMS experience an increase in the energy cost of walking, and showed that the higher cost of walking is significantly related to spasticity in the lower extremities, but not significantly related to lower extremity or trunk weakness. This may explain why the subjects in the studies by Newman et al. (2007), Dettmers et al. (2009) and Gervasoni et al (2014) continued to experience fatigue despite their increase in walking.
endurance, suggesting that pwMS can improve their endurance with continuous walking, but they may continue to feel the same level of fatigue. This study suggests that if there was a way to decrease fatigue when walking, pwMS could walk further distances and experience even greater gains in endurance. This idea suggests the need for a less-taxing method of gait training that manages the energy cost of walking in order to reduce fatigue.

A limitation of many of the aforementioned studies is that gait training was performed on a treadmill, and may not accurately reflect results if the exercise included more real life parameters. Walking over the ground involves self-propulsion of one’s body weight through space whereas treadmill walking involves moving the limbs to maintain one’s position on the machine. This creates differences in gait mechanics as well as in the energy requirements of the task. When considering walking as a functional training protocol, people walk over the ground to get from point A to point B; the adaptations resulting from treadmill training may have limited carryover into real world function. In spite of these limitations, the results do suggest a solid relationship between exercise capacity and gait training in pwMS. Fatigue, however, remains the limiting factor to achieve a greater volume of gait training.

To accurately study and report on walking endurance and the benefits of a gait training protocol, researchers must use reliable reporting tools. The 6MWT is a proven and reliable measure of ambulatory capability and endurance in pwMS. Goldman, Marrie, and Cohen (2007) investigated the correlation of the 6MWT to disability and subjective measures of fatigue, health status, and ambulation in subjects with MS. A single four hour study was performed, during which subjects performed three 6MWT tests taking one hour rests between each walk. The 6MWT correlated strongly with disability measurements calculated by the Multiple Sclerosis Functional Composite (MSFC) and the EDSS. In addition, the 6MWT correlated more strongly
to self-reported measures of fatigue, physical health status, and perceived walking ability than did the EDSS and MSFC. Savci et al. (2005) examined the relationship between performance on a 6MWT and measures of disability (EDSS), resting heart rate, fatigue (FSS), and limitations of activity in daily living (Barthel Index, BI) in thirty ambulatory pwMS. Resting heart rate, FSS values, and BI scores were each significant predictors of performance on the 6MWT. The 6MWT distances were inversely proportional to EDSS scores. These findings justify the 6MWT as a reliable diagnostic tool, and therefore make it an excellent means for measuring the effects of a gait training program for pwMS.

**INTERMITTENT TRAINING (IT)**

Intermittent training as a means of minimizing fatigue during exercise has been studied in both disabled and healthy populations, albeit on a limited basis. Studies involving pwMS indicate outcomes related to increased distance walked and decreased fatigue after performing intermittent exercise (Mansour, Atya, & Aboumousa, 2013; Karpatkin, 2006; Karpatkin and Rzetelny, 2012; Karpatkin et al., 2012).

Mansour, Atya, and Aboumousa (2013) explored the potentially less taxing method of gait training by comparing the effects of intermittent treadmill training with 40% body weight support and without body weight support on 24 pwMS and cerebellopyramidal involvement. Each subject completed 18 training sessions over a six week period consisting of a total of 15 minutes of treadmill walking (either body weight supported or unsupported). Subjects walked in five minute intervals, with five minutes of rest in between each interval. Both the body weight supported group and the group without body weight support had significant improvements in the Timed Up and Go Test, Overall Stability Index (OSI), stride length, and cadence after the training protocol, indicating that intermittent treadmill training has a positive effect on balance
and gait kinematics in pwMS. The body weight supported group had significantly greater improvements than the unsupported group across all outcome measures, which the authors explained could be because body weight supported training enabled subjects to practice walking with improved locomotor coordination and efficiency. This suggests that intermittent training and reduction of body weight decreased the energy cost of walking, as discussed in Olgiati et al. (1988), which allowed for significant improvements in gait. Functional carryover, however, may be limited, as improvements may not translate to full body weight walking. There remains a need for an intermittent training program performed without body weight reduction to allow for greater functional carryover.

Another successful intermittent gait training program was implemented by Karpatkin (2006). In this single case study, a 57 year old man with moderate disability (EDSS 4.5) due to MS began a walking program to improve his endurance and minimize fatigue. The training protocol included a six week training period wherein the subject walked every other day at a fast but comfortable pace for two minutes, followed by a one minute rest period, then again by a two minute walk, etc. The only measure of fatigue used was the patient’s verbal subjective feeling of fatigue. The subject significantly improved in distance walked during the 6MWT, progressing from 734 ft to 1056 ft by the end of the study with a lower subjective feeling of fatigue (not quantified). Karpatkin and Rzetelny (2012) further investigated the effects of an intermittent versus continuous walking on subjective feelings of fatigue in pwMS using a repeated measures crossover design. Participants reported for data collection on two occasions, one week apart, where they performed six minutes of either continuous or intermittent walking. Results, measured by the VASF, showed that subjects experienced significantly less fatigue during intermittent walking than during continuous walking. There was no effect noted for disease
severity, duration, or subject mood. Distance walked during the two conditions was not measured.

Karpatkin et al. (2012) utilized a randomized crossover design to compare distance walked and fatigue in 27 individuals with MS performing intermittent and continuous exercise. Specific exercise protocols were as follows: subjects were randomly assigned to either a continuous exercise or intermittent exercise group; the continuous exercise group performed a 6MWT with distance measured every two minutes; the intermittent exercise group walked a total of six minutes, resting for two minutes after every two minutes of exercise. Subjective feelings of fatigue before and after each walking condition were measured with the VASF. One to two weeks later, the subjects returned and switched groups (i.e. continuous group was now intermittent group, and intermittent group was now continuous group), and walked whatever way they did not walk initially. The total 6 minute distance walked was significantly greater in the intermittent group as compared to the continuous walking group. In addition, the distance walked during the last two intervals relative to the first was greater when subjects walked intermittently. Subjects reported decreased levels of fatigue after intermittent walking only. This suggests that intermittent walking is applicable as a treatment protocol to maximize the benefits of physical activity on walking endurance while diminishing the limitation of fatigue within pwMS.

Research into intermittent training is not limited to MS populations. Clapp and associates (1999) evaluated low intensity intermittent exercise in nine subjects with CFS. A pretest survey showed that the subjects were not confident in their ability to complete 30 minutes of exercise. They were, however, able to use intermittent exercise successfully by performing shorter durations of exercise interspersed with rest periods over the course of 60 minutes. Ten three-
minute exercise sessions, separated by three minutes of rest were performed at a self-selected pace on a treadmill. Measures of HR, VO2, and RPE were taken after performing intermittent exercise. Results showed no negative or limiting effects on these outcome measures indicating intermittent exercises as a viable means of avoiding exercise related fatigue.

Sabaphthy, Kingsley, Schneider, Adams, and Norris (2004) examined responses to an intermittent exercise program in patients with Chronic Obstructive Pulmonary Disorder (COPD). A single group of ten subjects performed both continuous and intermittent exercise non-consecutively. The continuous exercise program consisted of a single 30 minute exercise session whereas the intermittent exercise program consisted of a 1:1 ratio of exercise to rest for 60 minutes. None of the participants completed the continuous exercise; however, eight out of the ten participants completed 60 minutes of intermittent exercise. Capacity for exercise was significantly increased with intermittent exercise to a level that could not be achieved with continuous exercise. This study demonstrates that exercise capacity can be increased in a population with a significant cardiovascular disability without inducing fatigue and subsequently ceasing the exercise.

In a study by Weltman et al. (2008), 15 non-obese and 14 obese individuals, all sedentary and healthy, participated in both continuous and intermittent exercise programs. Outcome measures of serum growth hormone levels, VO2max, and serum lactate threshold were measured every ten minutes over a 24 hour period. The exercise protocol involved either a 30 minute session (continuous group) or three ten minute bouts (intermittent group) of treadmill walking. Multiple short exercise bouts distributed throughout the day were found to be as effective as a single continuous exercise bout for improving VO2max, lactate threshold, and growth hormone levels. If, in a healthy population, both intermittent and continuous training are effective in
improving measures related to walking endurance, intermittent walking could be as effective or more so in populations with MS.

The studies by Mansour, Atya, and Aboumousa (2013); Karpatkin (2006); Karpatkin and Rzetelny (2012); Karpatkin et al. (2012); Sabapathy et al. (2004); and Weltman et al. (2008) provide strong evidence to suggest intermittent training can improve endurance and minimize fatigue in healthy and non-healthy populations, including MS. The drastic improvements seen in non-MS populations with intermittent training further help demonstrate its effectiveness.

DETRAINING

Current literature presents conflicting information on the appropriate detraining period ranging from three, four, six, eight, and up to 24 weeks and involve both MS and non-MS populations (Vanden Berg et al, 2006; Chiara et al 2006; Triche and Lo 2008; Rampello et al. 2007; Sabapathy et al., 2011; Häkkinen 2000).

A four week detraining period has been found to provide sufficient detraining within research studies performed by Van den Berg et al (2006) and Chiara et al (2006). Van den Berg et al. compared aerobic training to no training in 19 pwMS in their randomized crossover study. The study encompassed four weeks of aerobic treadmill training performed three times per week for a half hour per day. Participants walked as far as they could, with duration of exercise being increased as tolerated to maximum of 30 minutes. Subjects were allowed a maximum of three rest periods of unspecified length. Results of aerobic training included an increase in speed and endurance with a reduction in fatigue as measured by the 10 Meter Walk Test, 2 Minute Walk Test, and FSS. After the four week detraining period, subjects’ outcome measures returned toward, but did not reach, baseline. This indicated that after four weeks some detraining will occur in pwMS but a longer time period may be needed for full return to baseline.
Chiara et al. (2006) examined the effect of expiratory muscle strength training (EMST) on maximal expiratory strength, pulmonary function, and maximal voluntary cough in pwMS with mild to moderate disability. Thirty-one subjects took part in the study: 17 with MS and 14 without MS who served as the control group. The subjects had eight weeks of EMST followed by four weeks of detraining. The main outcome measures were: Forced Vital Capacity (FVC), Forced Expiratory Volume (FEV), Peak Expiratory Flow (PEF), maximal voluntary cough, and Maximal Expiratory Pressure (MEP). All outcome measures were tested before training, after training, and after the detraining period. Prior to training, subjects presented with low MEP, FVC, FEV, and PEF when compared to the healthy subjects. After training, the MEP and PEF dramatically increased in all subjects. Interestingly, this study found a correlation between detraining and EDSS score. Seven subjects with an EDSS score of moderate disability (4.0-6.5) experienced significant improvement in cough airflow and were able to maintain it even after the four week detraining period. Ten subjects with an EDSS score of mild disability (0.0-3.5) who showed lower improvement in cough airflow after training were not able to maintain their values after the four week detraining period and instead returned to baseline. This study provides evidence suggesting EDSS score should be considered when determining the length of the detraining period. Both this study and Van den Berg et al. (2006) suggest that, for specific outcome measures, a four week detraining period may be sufficient for a complete return to baseline. It is important, however, to investigate longer detraining durations.

Triche and Lo (2008) implemented a six week detraining period in their randomized crossover study investigating whether robot assisted body weight supported treadmill training (BWSTT) was superior to BWSTT in pwMS. The treatment sessions encompassed six 40 minute sessions spanning three weeks, followed by the six week washout period. Measurements
taken before and after training included the 25 Foot Walk Test, 6MWT, EDSS, double support time, and step length ratio. Results of the study indicated no significant differences between treatment groups, with significant improvements on gait outcomes and EDSS scores. The authors concluded, based on outcomes in gait that a six week washout period was not sufficient to allow for full return to baseline. However, they postulated that the lack of detraining may have been caused by other training effects such as improved confidence and balance. There should be further investigation into the use of longer detraining periods.

Rampello et al. (2007) in their randomized crossover study comparing the effect of aerobic training and neurological rehabilitation on exercise capacity used an arbitrary eight week detraining period. The authors utilized lung function tests, respiratory muscle strength, 6MWT, and cardiopulmonary tests as outcome measures. Both training protocols improved exercise capacity and QOL scores measured by the MSQOL 54 scale. Authors reported non-significant differences between baseline measurements taken prior to the two interventions indicating that full detraining occurred within the eight week detraining period. This study had a high dropout rate of 26%, however, which could have been due to the length of the detraining period. This study indicates an eight week washout period is sufficient for detraining and a return to baseline with respect to walking endurance; however, this study does not provide conclusive evidence that eight weeks is the minimum amount of time necessary for full detraining and poses the risk of subject drop out due to time constraints.

Sabapathy et al. (2011) similarly utilized an eight week washout period in their crossover study comparing resistance training verses aerobic training programs. The primary outcome measure was the Modified Fatigue Impact Scale with secondary measurements of 6MWT, Timed Up and Go, functional reach, grip strength, and four step square tests. The only measure to
return to baseline was the measure of fatigue; however the authors did not compare baseline measures of any other outcome. Based on these results, it remains unclear if a detraining period as long as eight weeks is necessary to completely eliminate carryover between two different training conditions.

To compare a short (three weeks) versus a long (24 week) detraining period, Häkkinen (2000) investigated detraining effects with a strength training regimen in non-disabled middle aged and older individuals. Strength was measured using a dynamometer and electromyogram (EMG) during concentric and isometric knee contractions. Measurements were taken before and after 24 weeks of training as well as after three weeks of detraining. Subjects then re-trained for 21 weeks followed by a 24 week washout period with measurements again taken before and after training and the washout period. A detraining period of three weeks resulted in minor changes in muscle strength as compared to a 24 week detraining period, which resulted in significant decreases in muscle strength. Neither detraining period allowed for full return to baseline for dynamometer strength measures. Maximal EMG readings returned to baseline after three weeks of detraining in the elderly population only. The middle-aged population’s EMG data returned to baseline after the 24 week detraining period. This study demonstrates some detraining can occur within a short amount of time, such as three weeks and yet other measures, such as knee extensor strength may require longer than 24 weeks to fully decrease back to baseline. Authors do not list outcome measures for any timeframe between the three week and 24 week detraining making it difficult to ascertain at what point detraining to baseline level for each outcome is complete.

Current literature is conflicted on the appropriate timeframe for detraining; however, it has been shown that detraining will occur after as little as three weeks (Häkkinen, 2000). Longer
time periods will allow for further and more complete detraining, but longer detraining periods may cause complications in certain populations with degenerative conditions. Within the present study that involves an MS population, a detraining period longer than four weeks posed risks in disease progression and possible environmental influence that would have occurred if training was extended into the summer months. A four week detraining period was chosen to provide adequate walking endurance detraining with limited adverse effects of this progressive disease.

SUMMARY

Review of the current literature found limited research conducted on intermittent walking programs for pwMS. Only two studies examined whether intermittent exercise resulted in better outcomes related to walking endurance and fatigue in pwMS when compared to continuous training. The purpose of this study was to provide quantitative data comparing an intermittent walking program with a continuous walking program in pwMS as measured by distance walked in six minutes. An intermittent walking program should yield greater gains in distance walked than a continuous program for the following reasons: First, it identifies the limitation imposed by fatigue, and second, it provides a way to work with persons whose ambulation is limited by fatigue. By allowing a person with MS to rest prior to reaching a critical level of fatigue, any functional limitation or potential injury brought on by fatigue is avoided. Based on past research performed by Karpatkin (2006), Karpatkin and Rzetelny (2012), Karpatkin et al. (2012), Mansour et al. (2013), and Sabapathy et al. (2004), it is hypothesized that persons with Multiple Sclerosis who perform intermittent exercise (groups Ia and Ib) will walk a greater distance in 6 minutes than the continuous exercise group (groups Ca and Cb). The null hypothesis is that groups Ca and Cb will walk the same or greater distance than groups Ia and Ib.
METHODOLOGY

SUBJECTS

Twelve subjects were recruited from a group of former patients (i.e. discharged from active program) of the principal investigator (PI), on a voluntary basis, to create a sample of convenience. Inclusion criteria consisted of a positive diagnosis of MS; ambulatory for at least 6 minutes with or without an assistive device such as cane, crutches, walker, or braces; no evidence of exacerbation in the last three months as defined by a treating physician; no orthopedic or cardiovascular condition that will interfere with ability to walk for 6 continuous minutes; and ability to read, understand, and sign an informed consent form.

PROCEDURE

All testing and training was performed during the fall and spring months to minimize heat related exacerbation of MS symptoms that might occur during the summer months. Walking for each assessment was performed at Hunter College's Brookdale Campus. Distance was measured using a Keson Road Runner, model RR112 measuring wheel. Subjects completed a 6MWT by walking in circular laps around the perimeter of the rotunda so as to minimize the slowing down effects of turning.

On the first day, two forms of informed consent, as approved by the CUNY Institutional Review Board (IRB), were obtained for the screening process and the exercise protocol itself. Afterwards, subject characteristics and demographics including age, gender, years since diagnosis, specific MS diagnosis, EDSS, FSS, use of anti-fatigue or anti-spasticity medication, and use of an assistive device were collected. Each subject then sat for 15 minutes to minimize fatigue. The subject then indicated current level of fatigue on the VASF. Immediately following the VASF, the subject performed a 6MWT to obtain a baseline measurement. The subject was asked to walk at their best comfortable pace, and was guarded by the PI throughout the entire
walk, as well as followed by a wheelchair. Distance measurements were taken each minute during the baseline 6MWT. Immediately following the 6MWT, the subject's VASF score was again measured and recorded. Subjects were given the option to have a seated rest in the wheelchair during the 6MWT if they were unable to continue and to perform the test another day. However, no subject was unable to complete a 6MWT. Once all baseline information was collected, subjects were randomized into two groups: Intermittent (Ia) and Continuous (Ca). Randomization was done by placing two slips of paper into a hat with one slip having the letter "I" and the other having the letter "C". Each subject reached into the hat and pulled out a slip of paper determining their initial group placement.

The training intervention began within one week after randomization. Training had three phases: A 4-5 consecutive week intervention (Ia) period where the subjects performed a total of eight non-consecutive sessions of 6 minute walks either intermittently or continuously, a 4 week washout period where no training occurred, and a second 4-5 week training (Ib) period where the subject performed whatever type of walking he/she did not perform the first time. Each subject began their training three days past their initial baseline assessment. The Continuous group performed six minutes of continuous walking as performed during the initial 6MWT. The Intermittent group performed six minutes of intermittent walking in three two minute increments with two minute seated rests in between increments. As in the initial assessment, distance was measured each minute, and the subject's VASF was measured immediately before and immediately after walking.

After completion of a subject's eighth training session, a post training 6MWT was performed following the same procedure as the initial assessment. Subjects then had a four week washout period where they were asked to not engage in any specific walking exercises. Subjects
then switched protocols (“crossed over”) where those who performed intermittent walking in the first trial now performed continuous walking and those who performed continuously now performed intermittently. The initial protocol was then repeated in the crossed over groups. Prior to the start of the new training protocol, a new baseline assessment was established using the 6MWT performed in the same manner as the initial assessment. All training followed the same guidelines established above in regards to the intermittent and continuous walking programs as well as the measurements and data collection. Following the last training session of the second four week cycle, all subjects were measured again using the 6MWT. A visual representation of this process can be viewed in Figure 1.
Day 1: Demographics, Characteristics, EDSS, FSS (n=9)

15 Minute Rest

VAFS, 6MWT

Randomized Allocation

First Baseline Phase (1 Day)

First Training Phase (8 Sessions)

Intermittent Group (Ia) – (n=6)
2 min walk, 3 min rest (3 cycles)

Continuous Group (Ca) – (n=3)
6 min continuous walk

Sessions 1-8: FSS, VAFS, Distance

Sessions 1-8: FSS, VAFS, Distance

Post Training Assessment: 6MWT

Post Training Assessment: 6MWT

Washout Phase (4 Weeks)

No data collected
(No exercise performed)

No data collected
(No exercise performed)

Groups Cross Over

Second Baseline Phase (1 day)

Second Training Phase (8 Sessions)

Intermittent Group (Ib):
2 min walk, 3 min rest (3 cycles)

Continuous Group (Cb):
6 min continuous walk

Sessions 1-8: FSS, VAFS, Distance

Sessions 1-8: FSS, VAFS, Distance

Post Training Assessment: 6MWT

Post Training Assessment: 6MWT

Figure 1: Methodology Flow Chart
EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; 6MWT, 6 Minute Walk Test; VASF, Visual Analogue Scale of Fatigue
RESULTS

DEMOGRAPHICS AND SUBJECT CHARACTERISTICS

Twelve subjects participated in the study and nine completed both training protocols. Three subjects dropped out due to scheduling difficulties. Five subjects completed all eight training sessions for both continuous and intermittent conditions, all nine completed eight training sessions of just the intermittent condition, three subjects completed seven continuous training sessions, and one completed six training sessions for the continuous training condition. This means subjects completed 96.5% of training. Of the subjects who completed the training, the mean age was 52.99 years (±12.58, range 41-75 years), the mean number of years since diagnosis was 17.33 years (±12.00, range 1-34 years), and mean EDSS was 3.39 (±1.96, range 1-6.5). Three subjects were male; six were female. Five subjects walked with an assistive device; four used anti-fatigue medications, and two used anti-spasticity medication. These values are summarized in Table 1.

Subject characteristics were further analyzed to assess possible effects on the 6MWT scores. Pearson correlations (2- tailed) were used to analyze the effects of EDSS, age, years since dx, FSS, and medications on the walking scores. No significant interactions were revealed.

| Age, mean (SD) | x 52.99, range 41-75 years (±12.58) |
| Gender | Male 3 | Female 6 |
| EDSS Score, mean (SD) | x 3.39, range 1-6.5 (±1.96) |
| Type of MS | PP 3 | RR 2 | SP 4 |
| Taking Anti-fatigue Meds | 4 |
| Taking Anti-spasticity Meds | 2 |
| FSS score, mean (SD) | x 4.32, range 3-6.56 (±1.28) |
| Years since dx, mean (SD) | x 17.33, range 1-34 years (±12.00) |

Table 1: Demographics and Clinical Characteristics of Participants (n=9)

MS, Multiple Sclerosis; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; RR, relapsing-remitting; SP, secondary progressive; PP, primary progressive
6 MINUTE WALK TEST SCORES

6 Minute Walk Test scores improved 143 ft after intermittent training, while decreasing 59 ft after continuous training. A repeated measures ANOVA indicated a significant difference between the two conditions $F(1, 8) = 9.634, p = .015$ (Figure 2). Subjects walked an average of 1278.4 ft on the pretest 6MWT for continuous training. The average posttest 6MWT value for continuous training dropped to 1219.32 ft. In comparison, the pretest 6MWT value for intermittent training was 1157.42 ft with a posttest average 6MWT value of 1300.44 ft. To better understand the changes in gait over the 6 minute walk test period, the 6MWT scores were further analyzed in terms of minute-by-minute differences for each testing condition, comparing pretest to posttest scores for the continuous condition, pretest to posttest scores for the intermittent condition, continuous pretest scores to intermittent pretest scores, and continuous posttest scores to intermittent posttest scores. Significant minute-by-minute differences between pre and posttest 6MWT scores were seen in the intermittent condition for minutes one through six (Table 2, figure 3). No significant differences were seen between the pre and posttest 6MWT scores.

Figure 2: Continuous vs Intermittent Pre & Post 6 Minute Walk Tests (Group Mean Values); 6MWT, 6 Minute Walk Test
scores for the continuous conditions for minutes one through six (Table 3, figure 4), or for comparison of the pretest scores for the intermittent and continuous conditions (Table 4, figure 5). Differences between minute-by-minute posttest scores for the continuous and the intermittent conditions approached significance (Table 5, figure 6). ANOVA values for each condition are displayed in Table 6. Pre and posttest 6MWT values for each subject, along with their initial training protocol, can be viewed in Table 7.

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<th>Pre &amp; Post 6MWT - Intermittent Training Minute by Minute Comparison (in ft)</th>
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Table 2: Intermittent Training Minute-by-Minute Pre & Posttest 6MWT (Group Mean Values); 6MWT, 6 Minute Walk Test

Figure 3: Intermittent Training Minute-by-Minute Pre & Posttest 6MWT (Group Mean Values); 6MWT, 6 Minute Walk Test
<table>
<thead>
<tr>
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<th>1</th>
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<tbody>
<tr>
<td><strong>Average Pretest</strong></td>
<td>216.68</td>
<td>217.65</td>
<td>216.15</td>
<td>211.88</td>
<td>209.75</td>
<td>206.38</td>
</tr>
<tr>
<td><strong>Average Posttest</strong></td>
<td>201.62</td>
<td>211.50</td>
<td>202.29</td>
<td>202.43</td>
<td>201.29</td>
<td>200.20</td>
</tr>
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Table 3: Continuous Training Minute-by-Minute Pre & Posttest 6MWT (Group Mean Values); 6MWT, 6 Minute Walk Test

![Graph](image-url)

Figure 4: Continuous Training Minute-by-Minute Pre & Posttest 6MWT (Group Mean Values); 6MWT, 6 Minute Walk Test
Table 4: Continuous vs Intermittent Training Minute-by-Minute Pretest 6MWT (Group Mean Values); 6MWT, 6 Minute Walk Test

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<tbody>
<tr>
<td>Continuous</td>
<td>216.68</td>
<td>217.65</td>
<td>216.15</td>
<td>211.88</td>
<td>209.75</td>
<td>206.38</td>
</tr>
<tr>
<td>Intermittent</td>
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<td>191.87</td>
<td>193.12</td>
<td>193.14</td>
<td>190.12</td>
<td>191.64</td>
</tr>
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</table>

Figure 5: Continuous vs. Intermittent Training Minute-by-Minute Pretest 6MWT (Group Mean Values); 6MWT, 6 Minute Walk Test
### Table 5: Continuous vs Intermittent Training Minute-by-Minute Posttest 6MWT (Group Mean Values)

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<tbody>
<tr>
<td>Continuous</td>
<td>201.62</td>
<td>211.50</td>
<td>202.29</td>
<td>202.43</td>
<td>201.29</td>
<td>200.20</td>
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<tr>
<td>Intermittent</td>
<td>214.72</td>
<td>218.66</td>
<td>217.73</td>
<td>218.56</td>
<td>214.10</td>
<td>216.67</td>
</tr>
</tbody>
</table>

6MWT, 6 Minute Walk Test

### Figure 6: Continuous vs Intermittent Training Minute-by-Minute Posttest 6MWT (Group Mean Values)

6MWT, 6 Minute Walk Test

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38
Table 6: ANOVA Values of Significance (Group Mean Values); 6MWT, 6 Minute Walk Test

Table 7: Pre & Posttest 6MWT per Subject per Training Protocol 6MWT, 6 Minute Walk Test

FATIGUE

Fatigue during the walking conditions was measured using the VAFS. The change between the two walking conditions was analyzed using a repeated measures ANOVA. No significant difference was found in VAFS scores between the two conditions F (1-8) =0.004, p= 0.952 (Table 8, figure 7).

Table 8: Continuous vs Intermittent Pre & Post Training VASF (Group Mean Fatigue Values); VASF, Visual Analogue Scale of Fatigue
MINIMAL DETECTABLE CHANGE

To establish the clinical significance of these results, it was necessary to determine the Minimal Detectable Change (MDC) for the 6MWT that best matched the population of pwMS used in the study. MDC is defined as the minimum value that marks a clinically significant increase or decrease in function. Learmonth et al. (2012) examined reliability, clinical significance, and precision of various mobility and balance assessments in pwMS. The authors found the 6MWT to be reliable when tested one week apart in pwMS with mean EDSS scores of 5.26. In this population, the Interrater Correlation Coefficient (ICC), a measurement of reliability, was 0.96 for the 6MWT, the MDC was 76.2 m (250.00 ft), and the Standard Error of Measurement (SEM) was 27.48 m (90.16 ft). If a subject's 6MWT distance increased or decreased by 250 ft, with an error of ±90.16 ft, this would be an indicator of significant clinical change.
In the present study, all subjects performing intermittent gait training demonstrated improvement in distance walked, ranging from 0.17 ft to 430.25 ft, with a mean increased distance of 143.02 ft. In terms of continuous gait training, three out of nine subjects improved on their 6MWT distance while six decreased in distance walked, with a mean decrease of 59 ft. Out of those who improved with continuous gait training the mean increase in distance was 108.08 ft, ranging from 35.5 ft to 163.75 ft. In the subset of the sample who decreased with continuous gait training, the mean decrease in distance was 142.78, ranging from 41.92 ft to 476.58 ft. The difference between the decrease in distance walked after continuous training and the increase in distance walked after intermittent training is 202 ft, which approaches the value stated here for clinical significance.

According to Learmonth et al. (2012), SEM values are relatively high in pwMS possibly because of the inherent variability in disease presentation. A wide variability in distance walked by subjects in the present study is evident within the conditions of intermittent and continuous exercise. Learmonth et al. (2012) found correlations in the literature between EDSS scores and the MDC. According to Learmonth et al (2012), a greater range in distance could result in unrealistic values for change in heterogeneous populations. A study conducted by Fry and Pfaller (2006) investigating MDC in pwMS with average EDSS scores of 3.6 found the value for MDC to be greater than that by Learmonth et al. at 106 meters. However, this present study uses a heterogeneous mix of pwMS with EDSS 1-6.5, therefore it is possible that with the current subject pool within the present study, this would be a very inflated measure of change.
DISCUSSION

Subjects walked a further distance on the 6MWT after participating in an intermittent gait training program than after a continuous gait training program by a statistically significant amount. This strongly supports the stated hypothesis in suggesting pwMS can increase their walking distance with intermittent training, and that it can be superior to training with continuous walking. These findings are consistent with a case study performed by Karpatkin (2006), during which the subject had a significant increase in distance walked on the 6MWT after a six week training period consisting of intermittent walking. These findings also agree with Mansour, Atya, and Aboumousa (2013) who found that when pwMS completed 18 sessions of treadmill walking for 15 minutes with two 5 minute breaks (both body weight supported and unsupported), they had improvements on their Timed Up and Go Test, Overall Stability Index (OSI), stride length, and cadence. Neither of these studies, however, compared intermittent walking to continuous walking as is done in the present study. The present study is the first, to our knowledge, that compares an intermittent walking program to a continuous walking program in pwMS as a training protocol.

Intermittent training allows for greater distance walked due to many factors: greater volume of walking, reduction of fatigue, and reduction of body temperature. Karpatkin et al. (2012) compared 6 minutes of intermittent walking to 6 minutes of continuous walking. Results indicated that pwMS could walk a greater distance in 6 minutes if they were allowed two 2-minute rest breaks, than they could while walking with no rest breaks. Likewise, in the current study, when the subjects trained with intermittent walking, they were able to cover a greater distance during each training session. This allowed them to achieve a greater volume of exercise than they were able to accomplish with continuous training leading to a greater training effect.
It is possible subjects were able to walk farther with intermittent training because the rest breaks minimized fatigue. Karpatkin et al. (2012) found that pwMS reported lower subjective levels of fatigue after walking intermittently as oppose to continuously. The current study did not show a significant difference in subjective measures of fatigue between the intermittent and continuous training protocols; however the rest breaks during the intermittent training limited motor fatigue thus allowing them to walk farther. According to Paty and Ebers (1998) there are two subcategories of MS fatigue: lassitude defined as a generalized feeling of exhaustion, and motor fatigue which occurs with repeated muscle contractions or continued motor activity. Walking is a continuous activity that involves repeated contractions of the muscles in the lower extremities, thus it can produce motor fatigue; however, limiting the duration of walking to two minute intervals separated by two minute rest periods made it possible to reduce or avoid significant motor fatigue.

In addition, the rest breaks may have allowed for each subject’s body temperature to decrease back to normal. A review of the literature has shown that an increase in body heat generated with exercise can create MS fatigue (Bakshi, 2003; Skjerbæk et al., 2012; Davis et al., 2010). This increase in body temperature may explain why the continuous walking protocol was not as effective in increasing distance walked on the 6MWT as the intermittent walking protocol. Being that even a minor change in body temperature can worsen MS fatigue (Davis et al., 2010), a lack of rest breaks will allow the body temperature to continue to rise, limiting the distance walked during each training session, and therefore limiting the volume of exercise performed. The two minute rests incorporated into the intermittent training sessions may have provided enough time to offset any increases in body temperature that may have occurred during the two minutes of walking.
Because intermittent gait training allowed subjects to attain a higher volume of exercise while mitigating the effects of fatigue and thermosensitivity, they had the opportunity for greater improvements in cardiovascular endurance as well as greater gains in lower extremity muscle strength and endurance. Previous literature supports the idea that exercise can improve function in pwMS by increasing muscle strength (Petajan et al., 1996, Romberg et al., 2004), cardiorespiratory function (Petajan et al., 1996, Kileff and Ashburn, 2003), and walking speed (Kileff and Ashburn, 2003, Romberg et al., 2004). Therefore, providing a way for the subjects to achieve a greater volume of exercise can allow them to achieve greater functional gains. By training with intermittent walking, subjects were able to walk farther, and thus exercise more. This increase in the volume of exercise that was attainable during their training sessions allowed them to achieve significantly greater distances on the 6MWT. In addition, because fatigue was limited during intermittent gait training, the subjects may not have experienced significant declines in their walking mechanics. This provided them the opportunity to train using their best available gait mechanics for the duration of the interventions, thus allowing for improvements in lower extremity motor control.

In the present study, close examination of VASF scores indicated that fatigue did not significantly change after performing intermittent exercise (Table 8, figure 7). This finding is not consistent with previous research on intermittent exercise in pwMS that has demonstrated a decrease in fatigue after intermittent exercise. Karpatkin et al. (2012) reported a decrease in VASF levels of fatigue after subjects walked intermittently as compared to when they walked continuously. Measuring fatigue using the VASF can result in variability due to its inherent subjective nature.
Disease presentation and progression makes it difficult to control for factors affecting perceived fatigue in pwMS. Feys et al. (2011) reported that subjective fatigue levels changed throughout the day in pwMS, with higher levels of fatigue reported during the noon and afternoon hours as compared with mornings. While levels of subjective fatigue varied during the day, subjects did not display gait variations during ambulation on the 6MWT. Morris et al. (2002) found a similar pattern when investigating gait changes and fatigue in pwMS in morning versus afternoon exercise sessions, finding that self-reported fatigue significantly increased in the afternoon, while walking patterns remained relatively consistent from morning to afternoon. The results of these studies suggest increased subjective levels of fatigue may not correlate to decreased performance on the 6MWT.

Interestingly, subjects decreased in the average distance walked after a continuous training program suggesting that continuous gait training could have a negative impact on ambulation in pwMS. All subjects increased their distance walked after their intermittent training, but only three out of the nine increased their distance walked after their continuous training. The causative factors may be due to any combination of the following: continuous walking being detrimental to pwMS due to accrual of fatigue and increased body temperature; detraining occurring for those who trained continuously after having previously trained intermittently; or several subjects’ completion of fewer than eight continuous training sessions.

As previously discussed, a continuous walking program may not allow a pwMS to complete a high enough volume of gait training to significantly improve walking endurance. This is because it does not limit accrual of fatigue and can result in increased body temperature leading to decreased nerve signal conduction (Bakshi, 2003; Skjerbæk et al. 2012; Davis, et al., 2010). Any increase in MS fatigue can potentially decrease distance walked during a 6MWT.
Although current literature does report an increase in distance walked following a continuous gait training program, these studies use treadmill walking to either train or measure walking endurance which may not translate to self-propulsion on an indoor floor surface (Dettmers et al., 2009; Newman et al., 2007). Additionally, none use the 6MWT to measure distance but instead use the 2 Minute Walk Test or 10 Meter Walk Test which may not provoke MS fatigue and may lead to false perceptions of walking endurance. If continuous walking does not allow for significant gains in walking endurance, a training program involving continuous walking could lead to either a minimal increase, no increase, or even a decrease in distance walked on a post training 6MWT. Within this study, only three out of nine subjects improved in distance walked after continuous training and only one of those increased more after continuous training than after intermittent training. All subjects increased their distance walked after training with intermittent walking. Additionally, with minute-by-minute comparisons on the pre and post continuous training 6MWTs, there were no significant differences among the subjects. There were, however, significant increases on a minute-by-minute comparison before and after intermittent gait training for all subjects. The information gathered supports the theory that continuous training may actually exacerbate MS fatigue thereby limiting any significant gains in walking endurance.

Detraining is another likely contributor to the distance decrease on the post continuous training 6MWT given the short duration of the implemented washout period. Research demonstrates some detraining occurring within a four week period (Van den Berg et al., 2006; Chiara et al., 2006) but several studies found detraining continuing to occur up to 24 weeks post intervention (Rampello et al., 2007; Sabapathy et al., 2011; Hakkinen, 2000). If four weeks was not adequate, subjects may have continued to decrease in the cardiovascular endurance and lower
extremity muscle strength needed to maintain previous 6MWT gains over the course of the final continuous four week training. This also helps to explain why the average initial 6MWT values are lower prior to intermittent training as compared to continuous training. Six out of the nine subjects trained intermittently as their very first training program (Table 7). This means that their first baseline 6MWT was performed prior to any gait training and their second 6MWT preceded their continuous training but occurred after their intermittent training. If the four week detraining period did not allow for full detraining and return to baseline, then subjects could have walked a further distance on the second baseline 6MWT than the first baseline 6MWT. Of the six subjects who began with intermittent training, four subjects walked a greater distance on their second baseline 6MWT than their initial baseline 6MWT. Two out of that four demonstrated a steady increase in distance walked from the initial intermittent training period that continued through the detraining period and continuous training resulting in a final post training 6MWT that was higher than any previous 6MWT distance measured.

Due to scheduling difficulties and the time limitations of the study itself, all subjects did not complete an equal number of continuous training sessions. Four out of the nine subjects completed less than eight sessions of continuous training. This is a possible contributing factor for the average decrease in distance walked on the post continuous training 6MWT. Subject 1 completed six out of the eight continuous training sessions but completed all of the intermittent training sessions. This subject decreased in distance walked after continuous training while increasing slightly on the post intermittent training 6MWT. Subject 3 increased in distance after both training programs with a greater increase after intermittent training after completing seven out of eight continuous intermittent training sessions and all intermittent training sessions. Subjects 8 and 9 completed seven continuous training sessions and all intermittent training
sessions. Both subjects increased their distance walked after both conditions, however, only subject 9 increased by a greater amount after continuous training. It is possible that completing fewer continuous training sessions was a contributing factor to the lower average distance walked on the post continuous training 6MWT, but is unlikely that it is a primary cause given that the five subjects who did complete all sessions in both training programs all decreased in distance walked after continuous training.

DETRAINING

Within the present study, subjects could have potentially been affected by either training condition: intermittent or continuous walking. The hypothesis was that those performing intermittent walking would improve their distance walked during the 6MWT compared to their baseline distance walked. Similarly, it was hypothesized that continuous exercise could result in excessive fatigue and lower performance, and therefore not produce significant improvements in distance walked during the 6MWT. Subjects presented differently in terms of fatigue and level of disability reflected by their EDSS scores. The advantage of a crossover design is that each subject acted as their own control, thereby allowing for easy comparison between training conditions. A detraining period, also referred to as washout period, was instated to minimize any carryover effect of the previous training program. No training occurred during the detraining period; subjects were instructed to continue their normal day to day activities. The purpose of this period was to allow each subject's exercise level to return to baseline. To determine an effective length of time for the detraining period, factors related to the potential effects of time progression and how that may affect pwMS must be considered. For pwMS, a detraining period that is too long allows for the possibility of symptom exacerbation and disease progression.
It is possible, given the results of this study, that four weeks was not sufficient for all subjects to adequately detrain and return to baseline. Upon completion of their initial training period, subjects entered a washout period with the end goal of returning toward their baseline distance walked on the initial 6MWT. If adequate detraining did not occur, it could influence the second training period. To determine if the subjects experienced a detraining effect, the initial pre-training 6MWT was compared to the second pre-training 6MWT. Five subjects did not sufficiently return toward their baseline initial 6MWT after the four week detraining period and four did. One subject returned within one foot of the baseline initial 6MWT and three others actually decreased their distance walked after the detraining period as recorded on their second pre-training 6MWT (Table 7). On average, the six subjects who did not detrain sufficiently walked 280.82ft more on their second baseline 6MWT with a range from 142.17ft to 496ft.

Four weeks appears to have been a sufficient detraining period for four out of the nine subjects that participated in the study. This suggests that a four week detraining period may have been too short for more than half of the subjects to return sufficiently toward their baseline indicating a longer washout period may be necessary in future studies. Current literature supports a variety of sufficient detraining durations including a four week detraining period (Vanden Berg et al., 2006; Chiara et al., 2006) and longer detraining periods of 8 weeks (Rampello et al., 2007; Sabapathy et al., 2011) and 24 weeks (Hakkinen, 2000). The present study’s use of a four week detraining period was strongly based on the avoidance of MS disease progression. Additionally, Rampello et al. (2007) noted a high dropout rate due to the length of their study with an eight week detraining period which was a risk to the present study as well due to time constraints.
LIMITATIONS

Given that the present study was a pilot study, the sample size was small, consisting of only nine subjects. The selection of subjects, however, was diverse with respect to age, EDSS score, years since diagnosis, and use of medications, which helped to offset the small subject pool. In addition, this study was not completely blinded with respect to the subjects because many of them had participated in previous studies involving intermittent training vs continuous training. If this had an effect on the results, it likely only affected the VASF and not distance walked. Subjects found it difficult to quantify their fatigue using the VASF because they were unsure what was meant by the word fatigue. As previously mentioned, fatigue can be experienced as lassitude or motor fatigue, or both. The VASF provides real time measurement for the subjective feeling of both lassitude and motor fatigue. It is important to note that it provides an objective measure of a subjective feeling. To objectively measure fatigue, endurance and strength measurements must be recorded. Within the present study, walking endurance is objectively measured via the 6MWT.

As mentioned earlier, due to scheduling complications, four out of the nine subjects did not complete all eight sessions of continuous training. Additionally, due to scheduling demands, the weekly training frequency for each subject varied, ranging from one to three times per week, as did the interval between the last training session and post 6MWT (2-3 days). Subjects were encouraged to perform all training and testing with the same footwear, but this was not strictly enforced during the training sessions.

A literature review found wide variability in appropriate detraining time frames. A four week washout period was chosen to limit any possible progression of MS disease in the subjects; however, as previously mentioned it is possible that four weeks was not sufficient for all subjects. Other limitations include the unpredictability of MS disease progression, and the
variability in day-to-day MS disease presentation. MS is a variable disease with varying presentations, and factors such as amount of sleep, diet, and ADL requirements each day could affect 6MWT performance. In addition, as previously mentioned, heat can affect symptomatology of MS, which in turn can affect ambulation ability. Therefore warmer or humid days may have resulted in shorter distances walked on the 6MWT.

CONCLUSION

SUMMARY OF EVIDENCE
In spite of the limitations, this study offers strong evidence to support the use of intermittent walking as opposed to continuous walking, specifically intermittent gait training, as an appropriate and effective treatment protocol for pwMS to improve gait endurance. Future studies will need to further explore the benefit of intermittent gait training in a larger sample size. Longer detraining periods should be considered but caution must be taken due to the progressive nature of the disease. Further research should be conducted into the use of intermittent training in regards to strength training since all studies to date focus on endurance training.

CLINICAL SIGNIFICANCE
This is the only study to our knowledge that suggests a non-pharmacological, non-orthotic intervention for diminished MS gait endurance. This present study provides strong evidence to support intermittent gait training as a means of increasing walking endurance in pwMS. This has implications in both Physical Therapy treatment and day to day patient management of MS. This is especially relevant considering that ambulatory status is a major concern amongst pwMS and clinicians treating that population (Heesen et al., 2008). Within a
Physical Therapy setting, clinicians can implement an intermittent gait training protocol with confidence that it will adequately allow pwMS to reach walking endurance goals. Additionally, pwMS can manage their fatigue throughout the day by learning to identify signs of fatigue and implementing rest breaks as they feel fatigue beginning.

Clinicians and pwMS often find treating MS fatigue challenging for many reasons. Smith, Hale, Olson, Baxter, and Schneiders (2013) explored the challenges of MS fatigue management from the perspective of six physical therapists (PTs), three occupational therapists (OTs), three MS society workers, and three neurologists that have had regular contact with pwMS for more than two years. These health care providers (HCPs) reported fatigue as a major symptom their MS patients experience which is difficult to address and treat due to its unpredictability and variability amongst individuals. Patients felt that fatigue affects their career, personal and professional relationships, and even their own self-image. The clinicians found it difficult to conceptualize MS fatigue due to its variability. Furthermore, patients can be resistant to treatment due to poor past experience, fear of worsening their disability, or embarrassment of their decline. The HCPs in this study refer to “barriers to implementation” where patients do not want to exercise in front of others because their fatigue makes them feel different from those around them (p. 737). These patients experience decreased motivation and a possible disinterest in exercise. The limited amount of research based evidence of exercise benefits lead some pwMS to believe that it could actually worsen their disease. The present study helps provide evidence to support the benefits of exercise in pwMS if fatigue is managed through intermittent training.

Smith et al., (2013) further described a conflict between HCPs when discussing endurance training as a means of decreasing cardiovascular related MS fatigue (typically PTs)
versus prioritizing daily activities to limit energy expenditure and reduce the onset of MS fatigue (typically OTs). This conflict negatively affects patients due to conflicting messages. A cohesive team is important for MS management; there cannot be conflicts that cause the patient to question the plan of care. Therefore, an education model describing MS fatigue and evidenced based management would be beneficial for all health care disciplines. The HCPs in the Smith et al., (2013) article felt they must be creative in exercise prescription based on lack of evidence supporting that intervention. These interventions rely heavily on personal experience, trial and error, careful observation, and communication with their patients rather than truly evidence based methods.

The aforementioned struggles and conflicts within health care teams demonstrate the importance of evidentiary support for a consistent plan of care that addresses all facets of MS. The present study provides strong evidence to support the use of intermittent gait training as a means to improve ambulation by limiting fatigue; something that is important to patients and clinicians. Strong evidence provides a solid basis for every plan of care and fosters confidence among HCPs and patients, which further contributes to compliance and progress of ambulatory function.
APPENDIX

APPENDIX A: TYPES OF MULTIPLE SCLEROSIS
(Taken verbatim from The National Multiple Sclerosis Society)

Relapsing-remitting MS (RRMS)
RRMS — the most common disease course — is characterized by clearly defined attacks of worsening neurologic function. These attacks — also called relapses, flare-ups or exacerbations — are followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely and there is no apparent progression of disease. Approximately 85 percent of people with MS are initially diagnosed with relapsing-remitting MS.

Secondary-progressive MS (SPMS)
The name for this course comes from the fact that it follows after the relapsing-remitting course. Most people who are initially diagnosed with RRMS will eventually transition to SPMS, which means that the disease will begin to progress more steadily (although not necessarily more quickly), with or without relapses.

Primary-progressive MS (PPMS)
PPMS is characterized by steadily worsening neurologic function from the beginning. Although the rate of progression may vary over time with occasional plateaus and temporary, minor improvements, there are no distinct relapses or remissions. About 10 percent of people with MS are diagnosed with PPMS.

Progressive-relapsing MS (PRMS)
PRMS — the least common of the four disease courses — is characterized by steadily progressing disease from the beginning and occasional exacerbations along the way. People with this form of MS may or may not experience some recovery following these attacks; the disease continues to progress without remissions.
APPENDIX B: CONSENT TO PARTICIPATE IN A SCREENING PROCESS

Hunter College
Program in Physical Therapy
City University of New York

Consent to Participate in a Screening Process

**Investigators:**
Herbert I. Karpatkin, PT, DSc.
Stefanie DiCarrado, SPT
Bridget Dungan, SPT
Elizabet Huallpa, SPT
Jacob Potrzeba, SPT
Hunter College, Program in Physical Therapy
City University of New York
212-481-5051

**Purpose and Background**
Dr. Herbert Karpatkin, PT DSc is a professor at Hunter College in the Physical Therapy Department. Stefanie DiCarrado, Bridget Dungan, Elizabeth Huallpa, and Jacob Potrzeba are doctoral students in the Physical Therapy Program at Hunter College. They are conducting a study examining the effects on fatigue and distance walked when persons with multiple sclerosis (MS) walk intermittently versus continuously. You are being asked to participate in the screening process to determine eligibility for this study that will help determine if one walking protocol is less fatiguing than another in persons with MS and whether it allows them to walk longer distances. You were selected for participation because you are a person with MS over 18 years of age who walks as a regular means of transportation. There will be an anticipated 15 subjects that will participate in this screening process. Your participation in the screening process is voluntary. You may choose to not participate from the start and you may choose to stop at any time during the process.

**Procedures**
On the first day, you will fill out a demographics questionnaire in Dr. Karpatkin's office, after which you will be interviewed by researchers to address any necessary follow up questions in order to determine if you are eligible for the study. Subsequent sessions will take place at the physical therapy department of Hunter College, at 425 east 25th street, basement level.

- The screening process will involve answering questions about your medical history including length of time with MS, medications, use of assistive devices for walking such as canes, walkers, or splints, and whether you have a history of non-MS complications such as a cardiac condition or orthopedic problems. The researchers will also look at information from your medical records such as your Expanded Disability Scale Score (EDSS) and MS Quality of Life score (MS QOL-54).
- If your responses indicate that you are eligible, you will be asked to participate in this study.
- If you are not eligible to participate, the information obtained from you during the screening process will be omitted from this study and shredded to protect your privacy.

None of the procedures or questionnaires in this study are experimental. The only experimental aspect of this study is the gathering of information for the purpose of analysis.

**Risks**
There are minimal risks to you for participating in the screening process of this study. The screening process will require a maximum of 15 minutes of your time. Confidentiality of the information will be safeguarded by de-identifying subjects and filing any identifying information in a locked cabinet located at Dr. Karpatkin’s private practice. All identifying information will be destroyed at the conclusion of the study. If deemed ineligible, or if at any time you choose not to participate, data will be destroyed. You have the choice to refuse to answer any item in any of the questionnaires or forms.

**Benefits**
There is no direct benefit to you resulting from the screening process.

**Alternatives**
The alternative to this study is nonparticipation without repercussions or penalties.

**Financial Considerations**
Other than the cost of travel to and from the Hunter College Brookdale Campus, there are no costs incurred by you for participation in the screening process.

**Confidentiality**
Strict confidentiality will be maintained. Knowledge of your identity and participation in the screening process will be limited to Dr. Karpatkin, the collaborating physical therapy students, and Hunter College Institutional Review Board. Information about your participation will only be disclosed in the event of an emergency requiring hospitalization, and in such a case will be disclosed to the treating hospital physician and your primary care physician. Under expected non-emergency circumstances, no individual identifying information about you will be disclosed. Where possible, all identifying references about you will be removed and replaced by a numeric code. Participation in this research is voluntary and involves minimal loss of your privacy. All questionnaires and data about you that will be used in computer analysis will have number codes rather than your name. Your name will not be recorded on the information or reported in any scientific paper or professional meeting to protect your identity. All data will be reported in aggregate (group) fashion at a professional meeting or in a scientific journal so that no one can identify any information about you. If data is used for a publication in the medical literature or for teaching purposes, no names will be used. A master list of code numbers as well as all other data pertaining to you and other subjects will be kept confidential by the researchers and will be stored in a locked file cabinet in the faculty research advisor’s office. Data that will be used for computer analysis will be kept on a flash drive and only researchers involved in this study and representatives of the Hunter College Institutional Review Board will have access to the records.
and information about this study. All original hardcopy data will be shredded seven years after completion of the study. The code key connecting names to numbers will be kept in the research office of Dr. Karpatkin. Confidentiality will be maintained to the extent allowed by law.

**Withdrawal**
You may terminate your participation from the screening process prior to the start or at any time during the process without penalty or repercussion.

**Contact Information**
If you have questions about the screening process, you can contact Dr. Karpatkin, at (212) 481-5051. You should contact the Hunter College Human Research Protection Program (HRPP) Office at hrpp@hunter.cuny.edu or 212-650-3053, if you have questions regarding your rights as a subject or if you feel you have been harmed as a result of your participation in this research.

**Signatures**
I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I give my consent to participate in the screening process to determine if I am eligible to participate in the research study. I have received (or will receive) a copy of this form for my records and future references.

____________________  ________________________________  ____________
Participant’s Name   Signature                          Date

____________________  ________________________________  ____________
Researcher’s Name    Signature                          Date
APPENDIX C: CONSENT TO PARTICIPATE AS A RESEARCH SUBJECT

Hunter College
Program in Physical Therapy
City University of New York

Consent to Participate as a Research Subject

Investigators:
Herbert I. Karpatkin, PT, DSc.
Stefanie DiCarrado, SPT
Bridget Dungan, SPT
Elizabeth Huallpa, SPT
Jacob Potrzeba, SPT
Hunter College, Program in Physical Therapy
City University of New York
212-481-5051

Purpose and Background
Dr. Herbert Karpatkin, PT DSc is a professor at Hunter College in the Physical Therapy Department. Stefanie DiCarrado, Bridget Dungan, Elizabeth Huallpa, and Jacob Potrzeba are doctoral students in the Physical Therapy Program at Hunter College. They are conducting a study examining the effects on fatigue and distance walked when persons with multiple sclerosis (MS) walk intermittently versus continuously. You are being asked to participate in a study that will help determine if one walking protocol is less tiring than another in persons with MS and whether it allows them to walk longer distances. You were selected for participation because you are a person with MS over 18 years of age who walks as a regular means of getting around/commuting. There will be an anticipated 15 subjects that will participate in this study. Your participation in this study is voluntary. You may choose to not participate from the start and you may choose to stop at any time during the study.

Procedures
On the first day, you will fill out a demographics questionnaire in Dr. Karpatkin's office. Subsequent sessions will take place at the physical therapy department of Hunter College, at 435 east 25th street, basement level. Testing will be performed individually. You will fill out two simple fatigue surveys, perform a timed walking trial, and then recomplete only one of the two fatigue surveys. Each session will last approximately 45 minutes on two occasions per week for 4 weeks followed by 4 weeks of no intervention and then another 4 weeks of timed walking.

The study procedures in detail are as follows:
- If you agree to participate in the study, you will complete a questionnaire with the researchers to determine if you are eligible for the study. The screening will ask questions about your medical history including length of time with MS, medications, use of assistive devices for walking such as canes, walkers, or splints, and whether you have a
history of non-MS complications such as a cardiac condition or orthopedic problems. The researchers will also look at information from your medical records such as your Expanded Disability Status Scale Score (EDSS) and MS Quality of Life score (MS QOL-54).

- If your responses indicate that you are eligible, you will be asked to participate in this study.
- If you are not eligible to participate, the information obtained from you during screening will be removed from this study and destroyed/shredded to protect your privacy.
- Once identified as an eligible subject, you will be asked to schedule a time to meet with Dr. Karpatkin and two to four of the collaborating physical therapy students.
- At that scheduled time, you will come to the physical therapy department at Hunter College. While resting for 15 minutes, you will complete two forms that will inquire about your level of fatigue; the first will evaluate your overall level of fatigue and the second will evaluate your level of fatigue at that moment.
- Within one minute of completing the second form, you will be asked to perform one of two walks: either a single 6-minute continuous walk, or, three, 2-minute walks separated by two-minute seated rests. The walks should be performed at your best comfortable pace. You will wear a gait belt and be guarded by Dr. Karpakkin for the entire walk. You will also be followed with a wheelchair by one of the collaborating physical therapy students for the entire walk. Immediately after completing the walk, you will again fill out the fatigue form that asks about your level of fatigue at that moment. The distance that you walk will be recorded every minute regardless of whether the walk was intermittent or continuous. You will be asked to perform this timed walk twice a week for the initial 4 week period.
- After the 4 week detraining period (no walking intervention during this time) during which there will be no intervention, you will return and perform whichever walk you did not perform during the first 4 weeks. If you performed the 6-minute continuous walk during the first 4 weeks, you will be asked to perform the three, 2-minute walks with 2-minute rest intervals during the second 4 week training period. If you performed the three, 2-minute walks with 2-minute rest intervals during the first 4 weeks, you will perform the 6-minute continuous walk during the second 4 week training period. As with the first 4 week period, immediately before and after the timed walk, you will complete the form related to your current level of fatigue. Distances will be measured in the same manner as previously. You will be free not to answer any item in any of the questionnaires or forms.
- At each visit, please bring with you any walking devices such as canes, walkers, splints etc. that you would normally use for walking. Please bring the same comfortable walking shoes to all sessions.
- The total time expected for each session is 45 minutes.

None of the procedures or questionnaires in this study are experimental. The only experimental aspect of this study is the gathering of information for the purpose of analysis.
**Risks and/or Discomfort**
There are minimal risks to you from participation in this study. You may experience some fatigue-related discomfort as a result of the either of the two walking protocols. Because fatigue is the most common symptom in persons with MS, it is important to note that any fatigue experienced may be characteristic of the disease itself, as opposed to a result of the testing conditions. The walking protocols of this study are not expected to worsen your fatigue, or any other aspect of your MS in any way. You will be asked to wear a gait belt and Dr. Karpatkin will walk beside you for the entire walk. You will also be followed by one of the physical therapy students with a wheelchair. Despite these safeguards, there is a chance that you could incur an orthopedic injury from the walking or that you may fall and get injured. If this should occur we will immediately contact your primary care physician and if necessary take you to the emergency room.

If you feel bothered or upset as a result of participation, or for any reason wish to not continue you may simply ask to stop and we will immediately end the procedure. You will be free not to answer any item in any of the questionnaires or forms.

**Benefits**
There may be no direct benefits to you as an individual. You may experience an increase awareness of your fatigue levels, and how they may vary based on different exercise protocols.

**Alternatives**
The alternative to this study is not to participate, without repercussions or penalties.

**Financial Considerations**
Other than the cost of travel to and from the Hunter College Brookdale Campus, there will be no costs incurred by you for participation in the study. You will receive an $80.00 MetroCard to cover your travel-related expenses. This money does not obligate you to continue the study if at any point you wish to stop. You may terminate your participation at any time and you will still receive this compensation.

**Confidentiality**
The data will be collected using the two fatigue surveys that you fill out and by measuring the distance walked within each timed walk. Strict confidentiality will be maintained. Knowledge of your identity and participation in this study will be limited to Dr. Karpatkin, the collaborating physical therapy students, and the Hunter College Institutional Review Board. Information about your participation will only be disclosed in the event of an emergency requiring hospitalization, and in such a case will be disclosed to the treating hospital physician and your primary care physician. Under expected non-emergency circumstances, no individual identifying information about you will be disclosed. Where possible, all identifying references about you will be removed and replaced by a numeric code. Participation in this research is voluntary and involves minimal loss of your privacy. All questionnaires and data about you that will be used in computer analysis will have number codes rather than your name. Your name will not be recorded on the information or reported in any scientific paper or professional meeting to protect your identity. All data will be reported in aggregate (group) fashion at a professional meeting or in a scientific journal so that no one can identify any information about you. If data are used for a
publication in the medical literature or for teaching purposes, no names will be used. A master list of code numbers as well as all other data pertaining to you and other subjects will be kept confidential by the researchers and will be stored in a locked file cabinet in the faculty research advisor’s office. Data that will be used for computer analysis will be kept on a flash drive and only researchers involved in this study and representatives of the Hunter College Institutional Review Board will have access to the records and information about this study. All original hardcopy data will be shredded seven years after completion of the study. The code key connecting names to numbers will be kept in the research office of Dr. Karpatkin. Confidentiality will be maintained to the extent allowed by law.

Withdrawal
You may terminate your participation from this study prior to the start or at any time during the study without penalty, repercussion, or loss of compensation.

Contact Information
If you have questions about the study, you can contact Dr. Karpatkin, at (212) 481-5051. You should contact the Hunter College Human Research Protection Program (HRPP) Office at hrpp@hunter.cuny.edu or 212-650-3053, if you have questions regarding your rights as a subject or if you feel you have been harmed as a result of your participation in this research.

Signatures
I have read (or have had read to me) the contents of this consent forms and have been encouraged to ask questions. I have received answers to my questions. I have received answers to my questions. I give my consent to participate in this study. I have received (or will receive) a copy of this form for my records and future references.

<table>
<thead>
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<th>Signature</th>
<th>Date</th>
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<table>
<thead>
<tr>
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APPENDIX D: SUBJECT DEMOGRAPHIC INFORMATION

Subject Demographic Information

Age: __________ Gender: M / F Date of Birth: __________________
Type of Multiple Sclerosis: ______________________________________________________
Year since diagnosis of Multiple Sclerosis: _________________________________
Expanded disability status scale (EDSS) Score: __________________
Fatigue Severity Scale (FSS) Score: __________________
Use of assistive device: _______________________________________________________
Use of anti-spasticity medications: ____________________________________________
Use of fatigue medication: ____________________________________________________

Questionnaire

1. Are you able to walk unassisted for 6 minutes with or without an assistive device?
   YES           NO

2. Do you have any orthopedic, cardiovascular, or pulmonary issues that would be
   compromised by talking or prohibit you from walking?
   YES           NO

3. Are you able to read and comprehend an informed consent document?
   YES           NO

4. Have you had evidence of an exacerbation in the past 4 weeks as determined by a
   neurologist?
   YES           NO

5. Have you received Methylprednisone treatment in the past 4 weeks?
   YES           NO

6. Do you have difficulty following simple commands?
   YES           NO
APPENDIX E: FATIGUE SEVERITY SCALE (FSS)

Fatigue Severity Scale (FSS)

Your Name__________________________________________________________

Date:________________________________Date of birth: ________________

This questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

***A low value (e.g. 1) indicates strong disagreement with the statement, whereas a high value (e.g. 7) indicates strong agreement.

**During the past week, I have found that:**

1. My motivation is lower when I am fatigued
   
2. Exercise brings on my fatigue.
   
3. I am easily fatigued.
   
4. Fatigue interferes with my physical functioning.
   
5. Fatigue causes frequent problems for me.
   
6. My fatigue prevents sustained physical functioning.
   
7. Fatigue interferes with carrying out certain duties and responsibilities.
   
8. Fatigue is among my three most disabling symptoms.
   
9. Fatigue interferes with my work, family or social life.

Total Score: ______

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<th>Agree</th>
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APPENDIX F: DATA COLLECTION SHEET

Test Results

Type of Walk:  6 MWT □  Training □  (Continuous □ OR Intermittent □ )

FSS Score:__________

Distance after 1” __________________________
Distance after 2” __________________________
Distance after 3” __________________________
Distance after 4” __________________________
Distance after 5” __________________________
Distance after 6” __________________________

Comments ____________________________________________
____________________________________________________
____________________________________________________
____________________________________________________
____________________________________________________
____________________________________________________
____________________________________________________
APPENDIX G: DATA TABLES

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<th>Subject #</th>
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<th>Age</th>
<th>Gender (M/F)</th>
<th>Yrs Since Diagnosis</th>
<th>MS Diagnosis</th>
<th>EDSS</th>
<th>Medications</th>
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Table 9: Subject Demographics & Characteristics

MS, Multiple Sclerosis; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; RR, relapsing-remitting; SP, secondary progressive; PP, primary progressive; 6MWT, 6 Minute Walk Test

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Table 10: Visual Analog Scale of Fatigue Scores per subject

VASF, Visual Analog Scale of Fatigue
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Table 11: Incremental & Cumulative Pre & Post 6MWT- Continuous Training (ft walked)
6MWT, 6 Minute Walk Test
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<th>Post Training (ft)</th>
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Table 12: Incremental & Cumulative Pre & Post 6MWT - Intermittent Training (ft walked)
6MWT, 6 Minute Walk Test
### Table 13: Continuous Training Variability Scores (ft walked)

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Table 18: Fifth Continuous Training Session Minute by Minute Variability
### Table 19: Sixth Continuous Training Session Minute by Minute Variability

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