# Effects and feasibility of virtual reality system vs traditional physical therapy training in multiple sclerosis patients

Matthew C Streicher, Jay L Alberts, Matthew H Sutliff and Francois Bethoux

# **Abstract**

**Background/Aims:** Traditionally, physical therapy for gait and balance training takes place in a gym setting, which may not fully reproduce situations in everyday activities. The Computer Assisted Rehabilitation ENvironment system provides an immersive virtual environment, allowing a simulation of complex conditions conducive to gait and balance training. The purpose of this study was to determine: (1) the feasibility and safety of using the Computer Assisted Rehabilitation ENvironment system for physical therapy sessions with multiple sclerosis patients, and (2) pre-post treatment changes observed with the Computer Assisted Rehabilitation ENvironment system compared to traditional physical therapy.

**Findings:** Data from functional outcome measures Berg Balance Scale, Timed Up and Go test, Timed 25-Foot Walk, and 6-Minute Walk Test were extracted from the medical records of 62 patients with multiple sclerosis who had at least three physical therapy sessions in either environment. Statistically significant within-group improvements were observed for all outcome measures in the physical therapy Computer Assisted Rehabilitation Environment system group (P<0.05), and only for Berg Balance Scale in the traditional physical therapy group. There was a significant between-group difference in favour of physical therapy with the Computer Assisted Rehabilitation Environment system for the Timed 25-Foot Walk (P=0.022).

**Conclusions:** The results suggest the Computer Assisted Rehabilitation ENvironment system is a safe and effective tool for physical therapy-led gait and balance training for individuals with multiple sclerosis.

**Key words:** ■ Balance ■ Chart review ■ Gait ■ Multiple sclerosis ■ Physical therapy

Submitted: 11 May 2017; accepted following double blind peer review: 9 May 2018

Matthew C Streicher

Research engineer, Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA

### Jay L Alberts

Director of Cleveland Clinic Concussion Center, Cleveland Clinic Foundation, Center for Neurological Restoration, Cleveland, Ohio, USA

## **Matthew H Sutliff**

Rehabilitation manager, Cleveland Clinic Foundation, Center for Neurological Restoration, Cleveland, Ohio, USA

#### Francois Bethoux

Director of Rehabilitation Services, Cleveland Clinic Foundation, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland, Ohio, USA

Correspondence to: Matthew C Streicher

Email:

streicm@ccf.org

ultiple sclerosis is a chronic disease, of autoimmune origin, which causes demyelination and axonal loss in the central nervous system, generally resulting in the progressive

generally resulting in the progressive accumulation of physical and cognitive disability over time (Compston and Coles, 2002). An estimated 400 000 people in the US have multiple sclerosis (O'Sullivan and Schmitz, 2007). Multiple sclerosis is one of the main causes of disability among young adults at the peak of their productive years (Zwibel and Smrtka, 2011). Indirect costs a year to employers can range from \$2000 when considering sick leave, disability, and workers' compensation, to almost \$20 000 when factoring in missed work time and underemployment (Parisé et al, 2013). In particular, individuals with multiple sclerosis frequently develop

limitations in their ability to ambulate (O'Sullivan and Schmitz, 2007).

The impact of walking limitations on activities and participation is demonstrated in a growing body of evidence. In a survey of over 1000 individuals with multiple sclerosis, individuals who were unemployed had significantly more problems with walking than did those who were employed, and walking limitations were most frequently cited as the reason for unemployment (Edgley et al, 1991). Kornblith et al (1986) constructed a causal model to explain employment status in patients with multiple sclerosis using path analysis, and showed that loss of mobility was the main factor predicting unemployment. Up to 75% of individuals with multiple sclerosis exhibit walking limitations over the course of their disease (Swingler and Compston, 1992). Approximately two

thirds of patients with multiple sclerosis will require an assistive device for ambulation, such as a cane or crutches, and some will use a motorised wheelchair as a result of fatigue, weakness, balance problems, or to assist with conserving energy (National Multiple Sclerosis Society, 2016). Recent data indicate multiple sclerosis patients identify lower limb function as the most important bodily function, outscoring both vision and cognition (Heesen et al, 2008).

Both gait and balance impairments have been well documented in individuals with multiple sclerosis. Gait dysfunction in multiple sclerosis is commonly associated with decreased gait speed, walking endurance, step length, cadence, and joint motion (Cameron and Wagner, 2011). From a balance perspective, people with multiple sclerosis exhibit altered postural control across several contexts of behaviour, including stance under challenging sensory conditions, leaning or reaching to the limits of stability, postural responses to a loss of balance, gait, and anticipatory postural adjustments (Cameron and Lord, 2010). Early identification of gait and balance impairments in multiple sclerosis patients provides an opportunity for intervention such as rehabilitation training aimed at optimising functional outcome and preventing complications such as falls (Martin et al, 2006).

Physical therapy is recommended for the management of mobility limitations in multiple sclerosis, of which walking and balance impairment are major components (Golding and Henze, 2012). Khan and Amatya (2017) conducted a review of systematic reviews on rehabilitation in multiple sclerosis, and found strong evidence for the benefits of physical therapy on activity and participation. Virtual reality (VR) has opened new opportunities for gait training, particularly with the development of widely available home VR systems. In general, the use of visual and auditory feedback has been found to be beneficial for gait training in multiple sclerosis (Baram, 2013). Encouraging results from small uncontrolled studies have been reported (Baram and Miller, 2006; Peruzzi et al, 2016), but there is still a paucity of evidence on the effects of VR-based training on gait and balance in multiple sclerosis.

In addition to the traditional motion capture technology and force plates found in most biomechanics labs, the Computer Assisted Rehabilitation ENvironment (CAREN) system immerses an individual into a virtual environment thanks to a 180-degree screen surrounding a platform in the centre of the lab that has the ability to move in six-degrees of freedom. The platform is free to change position as forward/backward (surge), up/down (heave), and left/right (sway) translation in three perpendicular axes, combined with changes in orientation through rotation about three perpendicular axes, often termed

yaw (normal axis), pitch (transverse axis), and roll (longitudinal axis). The platform is equipped with an instrumented dual-belt treadmill (Figure 1). The ability of the platform to move synchronously with the VR images adds to the challenge by introducing situations that may occur in the free-living environment, such as walking uphill or downhill or balancing on an unsteady or moving surface. Kalron et al (2016) examined the efficacy of a 6-week balance training programme comparing the CAREN intervention to a conventional balance exercise programme, and concluded that the CAREN system was an effective method of balance training for individuals with multiple sclerosis. To our knowledge, the use of the CAREN system in outpatient physical therapy for gait and balance training has not been investigated.

Patients with multiple sclerosis have been using the CAREN system as a part of their course of physical therapy in the Cleveland Clinic Mellen Center since September 2013. Validated outcome measures of walking and balance are routinely administered before and after the course of physical therapy to assess treatment effects. The aims of this retrospective chart review study were to assess the feasibility and safety of physical therapy using the CAREN system, and to compare the outcomes of the CAREN system to those of traditional physical therapy in a gym setting.



Figure 1. CAREN system setup

This study was a retrospective chart review including patients with multiple sclerosis who were seen at the Cleveland Clinic Mellen Center between 1 September 2013 and 1 February 2016. The study was approved by the Cleveland Clinic Institutional Review Board (study number 15–833).

## Study participants

Inclusion criteria were as follows:

- Were 18 years of age or older
- Had a documented diagnosis of multiple sclerosis established by a neurologist based on the 2010 revised McDonald diagnostic criteria for multiple sclerosis (Polman et al, 2011)
- Had completed at least three physical therapy sessions either on the CAREN system or in a traditional physical therapy setting during the defined time frame
- Had at least one documented functional outcome measure before and after the course of physical therapy.

Subjects were excluded from the study if they had a neurological condition other than multiple sclerosis or a clinically significant orthopaedic or medical comorbidity that would interfere with the interpretation of the results.

#### **Treatment**

Physical therapy sessions lasted approximately 60 minutes regardless of the setting. Traditional physical therapy in a gym consisted of stretching, balance and gait training, and strengthening exercises. During exercise on the CAREN system, four applications were commonly used for gait and balance training (*Figure 2*), occasionally with additional gait or balance exercises

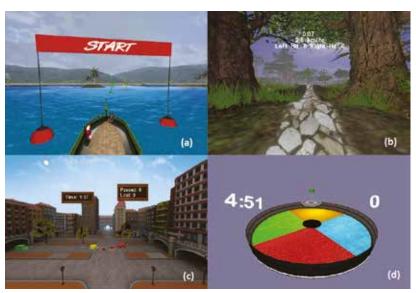


Figure 2. Virtual reality screen of four applications run on the CAREN system: a) Boat, b) Road, c) Traffic jam, d) Physics box

on the system based on the therapists' recommendation. All patients who received therapy on the CAREN system were fitted with a full-body harness and were accompanied by a physical therapist onto the movable platform to provide verbal and tactile cuing to enhance gait and balance, and to ensure that there were no safety concerns.

#### **Outcome measures**

The results of four functional tests routinely administered during physical therapy evaluations were analysed: Berg Balance Scale (BBS), Timed 25-Foot Walk (T25FW), Timed Up and Go test (TUG), and 6-Minute Walk Test (6MWT). The BBS is a 14-item test, looking mostly at standing balance (Berg et al, 1992). This test was originally developed to assess the risk of falling in elderly people, and scores below 45 (maximum score 56) were associated with increased fall risk in this population.

The T25FW is a measure of maximum gait velocity on a short distance. Typically an individual will walk the 25-foot distance as fast as possible, but safely, with the timer starting when the foot crosses the starting line and ending when the front foot crosses the 25-foot line.

The TUG test is a measure of dynamic balance in which an individual stands up from a chair, walks 3 metres, then turns around and walks back to the chair and sits down. The individual is timed from the moment their pelvis lifts off the chair until their pelvis reaches the chair again when sitting down.

The 6MWT is a measure of both gait velocity and endurance, where the total distance walked in 6 minutes is measured. The 6MWT is able to discriminate between healthy individuals and those with multiple sclerosis (Potter et al, 2012).

These tests were administered during the first assessment visit before the patient started physical therapy on the CAREN System or in the gym, as well as at the final session. The outcome measures used in this study have been shown to be reliable in multiple sclerosis (Learmonth et al, 2012).

# **Statistical analysis**

Descriptive statistics were generated as appropriate. The paired t-test was used to compare functional outcome measures before and after the physical therapy intervention (within-group change). Between-group comparison of change in outcome measure scores were tested with an analysis of variance. The significance level was set at P<0.05. In addition, effect sizes were calculated and the differences observed were compared to published minimum clinically importance difference values (Potter et al, 2012), to assess clinical significance. The percentages of patients satisfying minimum clinically importance difference values were compared between groups using a Chi-squared analysis.

#### **RESULTS**

# **Participant characteristics**

From September 2013 to February 2016, 62 patients met the inclusion criteria and were included in the analysis. Demographics and clinical characteristics for the study participants are listed in *Table 1*. There was no significant difference between the two groups regarding duration of the disease (P=0.70)as well as the amount of training each group had (P=0.06). Not all of the patients completed all of the functional outcome measures due to time constraints or individuals declining to complete the measure that day. No significant differences were observed between the Caren system and traditional physical therapy groups for the baseline measurements in each of the four outcome measurements. Measurements were taken before the intervention, and then again on the last scheduled day of therapy at the beginning of the session to avoid fatigue effects.

# Within-group changes

Average values for the outcome measures were calculated at both the beginning and the end of the treatment ( $Table\ 2$ ). There was a statistically significant improvement on the BBS between baseline and at the end of treatment, both for patients who received traditional physical therapy (n=25, P<0.001, d=0.41), and for patients who received therapy in the CAREN system. (n=31, P<0.001, d=0.44). The TUG task showed minimal change after traditional physical therapy (n=28, P=0.98, d=0.055), while CAREN users had a significant improvement (n=33, P=0.0021, d=0.29).

The within-group difference on the T25FW was not statistically significant after traditional physical therapy (n=27, P=0.42, d=0.001), while there was a statistically significant improvement after CAREN physical therapy compared to baseline (n=33, p=0.0048, d=0.28). There was actually a slight decrease in performance in the 6MWT after traditional physical therapy, but this change was not significant (n=12, P=0.74, d=0.038). By contrast, CAREN users showed a statistically significant improvement (n=18, P=0.0012, d=0.34).

No significant between-group differences in the percentage of patients meeting minimum clinically importance difference values were found (*Table 3*). Minimum clinically importance difference values for each measure were taken from the Multiple Sclerosis Outcome Measures Taskforce Multiple Sclerosis EDGE document (Potter et al, 2012) and other references: a change of 3 points on the BBS (Gervasoni et al, 2017), a 23% improvement for the TUG (Nilsagard et al, 2007), a 20% improvement for the T25FW (Coleman et al, 2012), and a distance change of 55.06 m for the 6MWT (Paltamaa et al, 2008).

Table 1. Demographics and clinical characteristics of participants (age, disease duration, and physical therapy sessions

	Traditional physical therapy (n=28)	CAREN physical therapy (n=34)
Gender, (women/men)	10/18	14/20
	Mean (standard deviation)	Mean (standard deviation)
Age (years)	49.6 (13.67)	49.2 (12.33)
Disease duration (years)	14.82 (10.33)	15.88 (11.25)
Type of multiple sclerosis	n	n
Relapsing remitting	13	22
Primary progressive	8	7
Secondary progressive	7	5
Assistive device		
Unilateral support (cane)	4	11
Bilateral support (walker, rollator)	10	7
No assistive device	14	16
Disease modifying therapy (yes/no)	20/8	24/10
Physical therapy sessions	10.59 (6.37)	14.97 (10.82)

# **Between-group differences**

Only the T25FW showed a statistically significant difference in baseline and post-treatment change between groups (F=5.54, P=0.022).

#### Safety

No safety issues were reported during physical therapy sessions in the CAREN system. Anecdotally, some of the visually stimulating environments displayed on the VR screen triggered mild dizziness in some patients. The issue was addressed by avoiding the specific application for that individual. Additionally, fatigue of motor function was sometimes reported and observed, and addressed by the physical therapist tailoring the workload for subsequent sessions.

## **DISCUSSION**

In this retrospective chart review study comparing the effects of physical therapy using the CAREN system to those of traditional physical therapy, no safety concerns were identified with the virtual environment, and tolerability was very good, although minor adjustments were sometimes needed to avoid dizziness. Statistically significant within-group improvements were observed on all walking and balance performance measures in the CAREN group, while only the balance (BBS) scores improved significantly in the traditional physical

Table 2. Change in functional outcome measures before and after treatment								
	Traditional physical therapy			CAREN physical therapy				
	Baseline (SD)	Post therapy (SD)	Difference (SD)	Baseline (SD)	Post therapy (SD)	Difference (SD)		
Berg Balance Scale	34.44 (11.67)	39.16 (11.65)	4.72 (5.70)*	36.10 (12.28)	41.32 (11.67)	5.23 (4.54)*		
Timed Up and Go (seconds)	15.55 (9.58)	15.54 (10.03)	-0.01 (3.13)	14.52 (6.41)	12.84 (5.77)	-1.67 (2.87)*		
Timed 25-Foot Walk (seconds)	11.50 (6.63)	11.14 (6.48)	-0.36 (2.30)	9.06 (3.44)	8.10 (3.28)	-0.97 (1.83)*		
6-Minute Walk (feet)	902.17 (503.53)	883.25 (498.70)	-18.92 (192.94)	1017.67 (323.84)	1125.39 (314.56)	107.72 (117.69)*		

<sup>\*</sup>statistically significant difference: P<0.05; SD: standard deviation

Table 3. Number of individuals who achieved a minimum clinically importance difference value for each outcome measure when comparing their baseline assessment to their post-therapy assessment

	Traditional physical therapy		CAREN physical	CAREN physical therapy	
	>MCID	<mcid< td=""><td>&gt;MCID</td><td><mcid< td=""></mcid<></td></mcid<>	>MCID	<mcid< td=""></mcid<>	
Berg Balance Scale	16 (64.0%)	9 (36.0%)	22 (71.0%)	9 (29.0%)	
Timed Up and Go (seconds)	7 (25.9%)	20 (74.1%)	6 (18.2%)	27 (81.8%)	
25-Foot Walk (seconds)	2 (7.1%)	26 (92.9%)	6 (18.1%)	27 (81.9%)	
6-Minute Walk (feet)	4 (33.3%)	8 (66.7%)	11 (61.1%)	7 (38.9%)	

MCID: minimum clinically importance difference

therapy group. Moreover, there was a significant between-group difference favouring CAREN training on the T25FW. No safety issues were identified while using the CAREN system for training.

Our findings regarding the feasibility and outcomes of using the CAREN system are consistent with those of other studies of VR in multiple sclerosis rehabilitation. In an uncontrolled study of 16 multiple sclerosis patients, Baram and Miller (2006) found that participation in VR treatment resulted in improved walking speed and stride length, with patients who were initially more impaired exhibiting greater benefits. Peruzzi et al (2016) reported a significant improvement of dual-tasking gait speed and stride length in 8 multiple sclerosis patients after receiving VR-based treadmill training for 6 weeks, and these benefits were retained 1 month after the end of treatment. In the study from Kalron et al (2016), 15 individuals with relapsing-remitting multiple sclerosis completed twelve 30-minute sessions of balance training on the CAREN system over a 6-week period, while another 15 individuals underwent conventional therapy consisting of stretching and balance training. For CAREN training, subjects were required to stand on a motion platform while maintaining their balance and advancing along a pre-defined virtual road, bounded on both sides by walls that were projected onto the screen, in front of the subject. The road itself was flat, straight, and hilly. The platform's movement was correlated with the visual stimulus. Post-training analysis looked at the centre of pressure trajectories during 30-second static stance tests with eyes open or closed. Clinical evaluations included a Functional Reach Test, BBS, Four Square Step Test, and the Falls Efficacy Scale International questionnaire. Both multiple sclerosis groups demonstrated a significant effect on clinical balance tests and two (out of eight) posturography measures. Additionally significant differences for the group by time interactions, in favour of the VR group were demonstrated in the Functional Reach Test and the Falls Efficacy Scale International questionnaire. The novel aspect of our study is that it looked at how the CAREN system can be used under the supervision of a physical therapist, combining gait and balance training.

These results suggest that the CAREN system can be used safely in individuals with multiple sclerosis, and that use of the CAREN system may lead to greater magnitude of improvement on functional performance tests. The CAREN system is engaging, unique, and challenging while providing the safety needed for the therapist to increase the complexity of gait and balance tasks. For example, the Road application (Figure 1b) allows patients to navigate a series of up and down slopes, and turns, that are more common to everyday outdoor walking than simply walking on level ground. The challenge of the tasks can be increased by adding upper extremity or cognitive dual tasks while walking, all in a harnessed and safe environment. In addition, the CAREN system allows multiple repetitions of tasks, including dual tasking, which can be more difficult to perform in a gym at the same level of intensity and safety. The CAREN system also has the ability to provide visual, somatosensory, and auditory feedback to users to help gauge improvement during their balance or gait tasks.

Anecdotal patient feedback also suggests that use of the CAREN system enhances their motivation. Patients report enjoying competing against their best time or score, which tends to make the training much more engaging and beneficial, and generally express a desire to use the CAREN system should they need physical therapy in the future. However, the immersive VR environment proves difficult to tolerate by some patients. Individuals who experience dizziness, vertigo, and visual issues could have difficulties adjusting to this kind of VR environment. Occasionally, activities such as the Boat (Figure 1a) may cause an individual to become dizzy or nauseated due to the combination of the moving screen and platform. To our knowledge, this is the first study reporting on the outcomes of gait and balance training supervised by a physical therapist in the CAREN system in an outpatient multiple sclerosis rehabilitation clinic.

#### **Limitations**

The main limitation of this study lies in the fact that it is a retrospective chart review, therefore group assignment was not randomised. The physical therapists may have selected patients to be trained on the CAREN system based on their clinical judgment regarding their potential to tolerate and benefit from the VR environment, as well as their ability to return for training visits. Baseline differences between the CAREN group and the traditional physical therapy group at baseline exceeded the reported minimum clinically importance difference values for both the T25FW and the 6MWT, in favour of the CAREN group, although the P values do not reach statistical significance. This may explain why the CAREN training group appeared to be higher functioning, even though none of the baseline differences were statistically significant.

Another study limitation was that the 'dosing' of the physical therapy interventions favoured the CAREN user group over the traditional therapy group, which may have favoured the outcomes for users of the CAREN system. The variability in the number of

sessions regardless of group was another limitation in this retrospective chart review. The sample size is relatively small, and the sample is not representative of the general population of patients with multiple sclerosis referred to physical therapy. Although this costly system cannot be applied on a large scale, it can serve as a model for the use of less expensive VR systems.

#### CONCLUSIONS

The results from this study suggest that the CAREN system, used under the guidance of a physical therapist, is a safe and effective training tool for individuals with multiple sclerosis, which provides an engaging and lifelike environment for gait and balance rehabilitation. Similar to traditional physical therapy, therapy sessions on the CAREN system can be tailored to individual needs and characteristics, and the applications allow a progression in difficulty during the course of treatment. The CAREN system facilitates the provision of real-time feedback, allows individuals to compete against themselves, and provides enhanced opportunities for task repetition and dual tasking without compromising safety. Based on these findings, a single-blind randomised controlled trial in individuals with multiple sclerosis and walking impairment, comparing traditional physical therapy gait and balance training with training on the CAREN system, with a fixed duration, frequency, and number of training sessions, and specific guidelines for session contents allowing for individualised progression of exercises is being planned as a follow-up to this research. Outcome measures will include clinical and self-report instruments, as well as motion analysis to better understand the impact of training on motor control. IJTR

Conflict of Interest: none declared.

Baram Y. Virtual sensory feedback for gait improvement in neurological patients. Front Neurol. 2013;4:138. https://doi. org/10.3389/fneur.2013.00138

Baram Y, Miller A. Virtual reality cues for improvement of gait in patients with multiple sclerosis. Neurology. 2006;66(2):178–181. https://doi.org/10.1212/01.wnl.0000194255.82542.6b10.1212/01.wnl.0000194255.82542.6b

Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. Can J Public Health. 1992;83(Suppl 2):S7–11.

Cameron MH, Lord S. Postural control in multiple sclerosis: implications for fall prevention. Curr Neurol Neurosci Rep. 2010;10(5):407–412. https://doi.org/10.1007/s11910-010-0128-010.1007/s11910-010-0128-0

Cameron MH, Wagner JM. Gait abnormalities in multiple sclerosis: pathogenesis, evaluation, and advances in treatment. Curr Neurol Neurosci Rep. 2011;11(5):507–515. https://doi.org/10.1007/s11910-011-0214-y10.1007/s11910-011-0214-y

Coleman CI, Sobieraj DM, Marinucci LN. Minimally important

- clinical difference of the timed 25-foot walk test: results from a randomized controlled trial in patients with multiple sclerosis. Curr Med Res Opin. 2012;28(1):49–56. https://doi.org/10.11 85/03007995.2011.63975210.1185/03007995.2011.639752
- Compston A, Coles A. Multiple sclerosis. Lancet. 2002;359(9313):1221–1231. https://doi.org/10.1016/S0140-6736(02)08220-X10.1016/S0140-6736(02)08220-X
- Edgley K, Sullivan MJ, Dehoux E. A survey of multiple sclerosis: II.

  Determinants of employment status. Can J Rehabil. 1991;4:127–
  132
- Gervasoni E, Jonsdottir J, Montesano A et al. Minimal clinically important difference of Berg Balance Scale in people with multiple sclerosis. Arch Phys Med Rehabil. 2017;98(2):337– 340. https://doi.org/10.1016/j.apmr.2016.09.12810.1016/j. apmr.2016.09.128
- Golding JC, Henze T. 2012. Recommendations on rehabilitation services for persons with multiple sclerosis in Europe. Rehabilitation in multiple sclerosis. https://www.eurims.org/images/stories/documents/Brochures/Recommendations%20 on%20MS%20Rehabilitation%20RIMS%20EMSP%202012. pdf (accessed 5 September 2018)
- Heesen C, Böhm J, Reich C et al. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. Mult Scler. 2008;14(7):988–991. https://doi. org/10.1177/135245850808891610.1177/1352458508088916
- Kalron A, Fonkatz I, Frid L et al. The effect of balance training on postural control in people with multiple sclerosis using the CAREN virtual reality system: a pilot randomized controlled trial. J Neuroeng Rehabil. 2016;13:10. https://doi.org/10.1186/ s12984-016-0124-y
- Khan F, Amatya B. Rehabilitation in multiple sclerosis: a systematic review of systematic reviews. Arch Phys Med Rehabil. 2017;98(2):353- 367. https://doi.org/10.1016/j. apmr.2016.04.01610.1016/j.apmr.2016.04.016
- Kornblith AB, La Rocca NG, Baum HM. Employment in individuals with multiple sclerosis. Int J Rehabil Res.1986;9(2):155–165. https://doi.org/377103610.1097/00004356-198606000-00006
- Learmonth YC, Paul L, McFadyen AK et al. Reliability and clinical significance of mobility and balance assessments in multiple sclerosis. Int J Rehabil Res. 2012;35(1):69–74. https://doi.org/10.1097/MRR.0b013e328350b65f10.1097/MRR.0b013e328350b65f

- Martin CL, Phillips BA, Kilpatrick TJ et al. Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. Mult Scler. 2006;12(5):620–628. https://doi.org/10.1177/135245850607065810.1177/1352458506070658
- National Multiple Sclerosis Society. 2016. Multiple sclerosis: just the facts. https://www.nationalmssociety.org/nationalmssociety/media/msnationalfiles/brochures/brochure-just-the-facts.pdf (accessed 11 September 2018)
- Nilsagard Y, Lundholm C, Gunnarsson L-G, Denison E. Clinical relevance using timed walk tests and the 'timed up and go' testing in persons with multiple sclerosis. Physiother Res Int. 2007;12(2):105–114. https://doi.org/10.1002/pri.35810.1002/ pri.358
- O'Sullivan SB, Schmitz TJ. Physical rehabilitation. 5<sup>th</sup> edn. Philadelphia, PA: FA Davis; 2007.
- Paltamaa J, Sarasoja T, Leskinen E, Wikstrom J, Malkia E. Measuring deterioration in international classification of functioning domains of people with multiple sclerosis who are ambulatory. Phys Ther. 2008;88(2):176–190. https://doi.org/10.2522/ptj.2007006410.2522/ptj.20070064
- Parisé H, Laliberté F, Lefebvre P et al. Direct and indirect cost burden associated with multiple sclerosis relapses: Excess costs of persons with MS and their spouse caregivers. J Neurol Sci. 2013;330(1-2):71–77. https://doi.org/10.1016/j. jns.2013.04.00710.1016/j.jns.2013.04.007
- Peruzzi A, Cereatti A, Della Croce U et al. Effects of a virtual reality and treadmill training on gait of subjects with multiple sclerosis: a pilot study. Mult Scler Relat Disord. 2016;5:91–96. https://doi.org/10.1016/j.msard.2015.11.00210.1016/j.msard.2015.11.002
- Polman CH, Reingold SC, Banwell B et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292–302. https://doi.org/10.1002/ ana.2236610.1002/ana.22366
- Potter K, Allen D, Bennett S. 2012. Report and recommendations of the APTA neurology section multiple sclerosis outcome measures taskforce.http://neuropt.org/docs/ms-edge-documents/final-msedge-document.pdf?sfvrsn=4 (accessed 5 September 2018)
- Swingler RJ, Compston DA. The morbidity of multiple sclerosis. Q J Med. 1992;83(300):325–337. https://doi.org/1631264
- Zwibel HL, Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care. 2011;17:S139–S145. https://doi.org/21761952