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Case Report

Rehabilitation with Neuromuscular Electrical Stimulation Leads to Functional Gains in Ambulation in Patients with Secondary Progressive and Primary Progressive Multiple Sclerosis: A Case Series Report

AUI ▶

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Abstract

Background: Gait disability in patients with secondary progressive multiple sclerosis (SPMS) or primary progressive multiple sclerosis (PPMS) rarely improves.

Primary study objective: This article reports on a case series of patients with SPMS and PPMS who were treated using neuromuscular electrical stimulation (NMES), a well-tolerated physical therapy (PT) treatment modality used to aid musculoskeletal recovery, coupled with a home-exercise program (HEP) to treat MS-related gait disability.

Setting: The setting for this trial was a PT private practice.

Patients: This trial was conducted with patients who had SPMS or PPMS with MS-related gait disability.

Case series description/intervention: Between June 2007 and June 2009, a licensed physical therapist (R.D.) used NMES coupled with a HEP to work with patients who had SPMS/PPMS and multiple sclerosis (MS)-related gait disability. All of the cases in which an NMES test session of NMES was conducted were included in the case series. Data regarding MS symptoms, treatment, gait, and function were abstracted from the PT clinic notes. Results of assessment with the expanded Kurtzke Disability Status Scale (EDSS) at presentation and at most recent visit were abstracted from the clinical record by the treating physical therapist (R.D.).

Clinical outcome/results: Nine (9) patients (7 with SPMS and 2 with PPMS) met inclusion criteria for review. Mean of years of diagnosis was 10.4 (range, 4–15), and mean EDSS score at presentation was 5.9 (range, 4.5–6.5). Mean of days of NMES was 140 (range, 22–495). Mean EDSS scores improved by 0.78 (range, 0–2.0).

Conclusions: NMES, an approved Food and Drug Administration treatment modality for muscle spasm, muscle pain, and disuse atrophy—all of which are commonly present in patients with gait disability associated with SPMS and PPMS—was associated with measurable gains in ambulatory function. Additional studies are warranted.

Introduction

MILD GAIT DISABILITY is common in patients with relapsing–remitting multiple sclerosis (MS). The more severe and progressive gait disability patients with secondary progressive MS (SPMS) or primary progressive MS (PPMS) rarely improves.

Neuromuscular electrical stimulation (NMES), a well-tolerated physical therapy (PT) treatment modality with minimal side-effects, has been used to aid musculoskeletal recovery postoperatively and for patients with stroke,^{1,2} cerebral palsy,^{3,4} severe congestive heart failure, or severe obstructive lung disease.⁵ Although specific numbers of frequency in MS are not available, the development of foot

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drop is common in gait impairments in patients with SPMS or PPMS.⁶ NMES is a Food and Drug Administration (FDA)-approved treatment for muscle spasm and atrophy, which are commonly present in patients with multiple sclerosis-related gait disability. The standard American diet is deficient in B vitamins, minerals, and essential fats,⁷ all of which are critical nutrients for generation of myelin and neurotransmitters as well as excretion of toxins.^{8,9}

A patient (W.T.) with SPMS requested and received NMES treatments for gait rehabilitation and had a marked gain in function using NMES; exercise; and intensive, directed nutrition to support brain metabolism and improve mitochondrial bioenergetics.¹⁰ Following the dramatic gains in function achieved with that patient, the treating physical therapist (D.R.) offered NMES, but not nutrition advice, to



FIG. 1. 300 PV Empi® device. Manufactured by Empi.

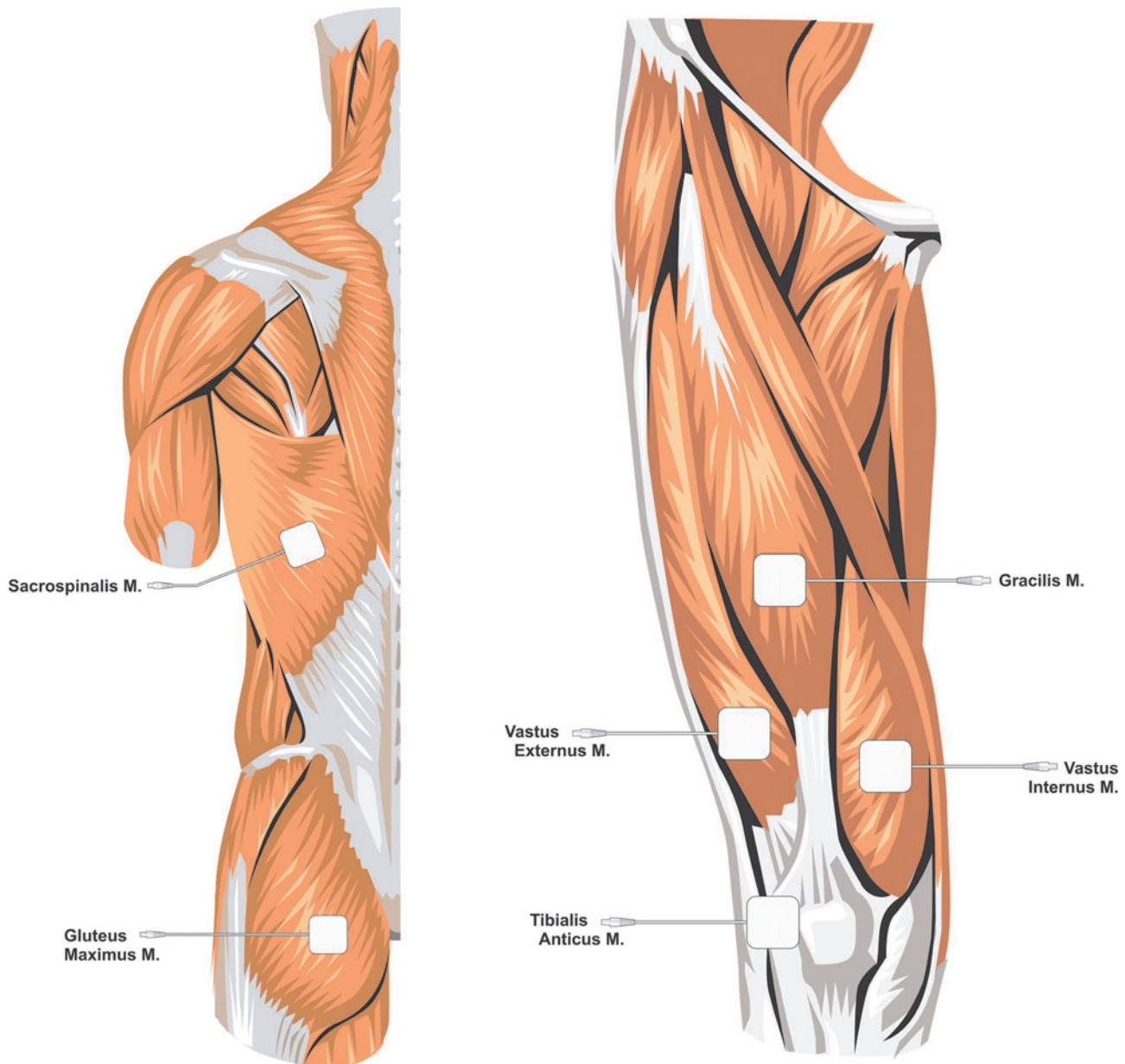


FIG. 2. Motor points for muscle groups with significant impact on ambulation.

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◀ AU7

NEUROMUSCULAR ELECTRICAL STIMULATION FOR MS

TABLE 1. DEVICE PREPROGRAM (PP) SETTINGS USED

Parameters	EMPI® 300 PV Stimulator Program				
Preset programs (PP)	PP1 Large muscle	PP2 Small muscle for dorsiflexion (tibia anterioris)	PP5 Gait training ^{1a}	PP6 Spasm reduction	Custom Small muscle
Wave form	Symmetrical (S)	Asymmetrical (A)	S	S	A
Ramp on (seconds)	2	2	NA	2	2
On time (seconds)	12	12	Continuous alternating between channels 1 and 2	10	5
Ramp off (seconds)	2	1	NA	2	2
Off time	20	20	NA	20	5
Pulse rate (Hz)	35	45	35	80	50
Pulse width	300 μ	300 μ	300 μ	300 μ	400 μ
Current (milliamps)	Patient control 30–50 usual dose	Patient control 30–50 usual dose	Patient control 30–50 usual dose	Patient control 30–50 usual dose	Patient control 30–50 usual dose

^aChannel 1 is active when the trigger (foot switch) is released and Channel 2 is active when the weight of the foot is applied to the foot switch.

NA, not applicable.

other patients with MS receiving therapy for MS-related gait problems. Thus, the authors tested the hypothesis that NMES and exercise would improve gait function in patients with SPMS or PPMS.

Materials and Methods

All cases in which a test session of NMES home exercise program (NMES-HEP) was completed are reported. Between June 2007 and June 2009, a licensed physical therapist (D.R.) used NMES as a treatment modality for 9 patients with MS. Specific nutrition advice was not part of the PT treatment. Data regarding MS symptoms, treatment, gait, and function were abstracted from the PT clinic notes. The motor testing (MMT) for lower extremities (LEs) at presentation, and the expanded Kurtzke Disability Status Scale (EDSS) at presentation and at most recent visit, were abstracted from the clinical record by the treating physical therapist (D.R.). See Appendix for definitions of EDSS scores. A test session of NMES was given in the clinic to the patients, all of whom reported moderate but tolerable discomfort during NMES. Those who were capable of operating the device safely at home were then instructed to use NMES to augment the NMES-HEP and were given a portable electrotherapy device (300 PV, manufactured by Empi).

The Empi® electrical therapy device was chosen because: (1) it is easy to use by laypeople; (2) it can be used to treat muscle spasm; and (3) it permits neuromuscular reeducation of both small and large muscle groups. The Empi electrical device also has a foot switch to facilitate gait retraining (by sequentially delivering electrically driven muscle contractions to muscles involved in ankle extension and flexion). The 300 PV Empi weighs 8 ounces and is 1.26"×3.3"×4.5" and is small enough fit either on a belt with a clip or in a large front pocket of a pair of pants (Fig. 1). Power is supplied by two AA rechargeable batteries. The device has dual channels, allowing two muscle groups to be trained simultaneously. Pulse width ranges from 50 to 400 μseconds. The

F1 ▶

wave form is symmetric square or asymmetric square and the amplitude ranges from 0 to 100 mAmperes according to patient tolerance. The electrical current is delivered through reusable electrodes placed over the motor points of muscles, which are to be strengthened (Fig. 2).

◀ F2

The device settings used by the patients are listed in Table 1. Patients were advised to use the NMES while completing their HEP-NMES and patients were also advised that that, optimally, 15 minutes of daily NMES were required to maintain muscle strength and 45 minutes of daily NMES were required for building muscle mass. Patients were also advised to add additional NMES sessions at a lower-intensity setting while completing activities of daily living. The specific program of NMES stimulation and progressive exercise was tailored to each patient, with emphasis on a program that the patient was capable of and willing to perform regularly, and that would improve ambulation. The preset programs were chosen based on whether the patient had more trouble with spasticity (in which case the spasm-reduction programs were used) or muscle weakness (in which case the large-muscle or small-muscle programs were

◀ T1

TABLE 2. PATIENT CHARACTERISTICS

Patient number	Gender	Age	Years since MS diagnosis	Type of MS
1	M	71	16	PPMS
2	F	53	21	SPMS
3	M	68	08	PPMS
4	F	37	05	SPMS
5	F	49	04	SPMS
6	F	55	09	SPMS
7	M	55	15	SPMS
8	M	44	11	SPMS
9	F	67	01	SPMS

MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

used, depending on the specific muscle groups stimulated). As the therapist became more familiar with the use of the foot switch as part of gait retraining, the gait switch was also used as part of the neuromuscular reeducation of the tibia anterioralis (the muscle controlling ankle dorsiflexion).

Results

Three (3) men and 6 women received a test session of NMES and had a diagnosis of either SPMS (7 patients) or PPMS (2 patients). The mean age was 55.44 (range 37–71); mean years of diagnosis was 10 (range 1–21); and the mean EDSS score was 5.9 (range 4.5 to 6.5; Table 2). The majority of patients required cane(s), walkers, and/or scooters for ambulation. One (1) patient was ambulatory without a cane or ankle foot orthosis. Days of NMES ranged from 22 to 495. One (1) patient was lost to follow-up, because of distance to clinic, after two clinic sessions. The mean change in EDSS for all patients was 0.778 (range 0–2.0), and, for the 6 patients (4 male, 2 female; 4 with SPMS, 2 with PPMS) who had more than 100 days of NMES, the mean improvement in EDSS was 1.0 (range 0.5–2.0). Notably, the number of days of NMES for all patients correlated strongly with the level of improvement in function as measured by the EDSS score ($Y = 0.0035x + 0.2182$; $R^2 = 0.9026$). Therapist observation of improved gait mechanics was reported in 7 patients (Table 3). Patient characteristics at presentation are shown in Table 1. Length of treatment, and outcomes are presented in Table 3.

Discussion

NMES is a Food and Drug Administration–approved treatment modality for treating muscle pain and muscle spasm and for reducing disuse-associated muscle atrophy, all of which are typical of patients with SPMS or PPMS. Exercise is associated with increased generation of nerve-growth factor, brain-derived neurotrophic factor, insulin-like growth factor, glial cell growth factor, and endorphins,^{11–15} all of which are critical for maintenance of muscle mass and/or repair of myelin and are diminished in SPMS, PPMS, and Parkinson's disease. NMES has been used to aid musculoskeletal recovery clinically. NMES has also been found to be superior to transcutaneous electrical stimulation (TENS) for relief of pain, improvement of range of motion, and functional improvement.¹⁶ Many researchers have reported that individuals who have severe fatigue disability from either cardiovascular^{16–18} or lung disease^{5,19} and who used NMES in conjunction with progressive exercise experienced statistically significant improvements in quality of life and had improved ambulation and mobility after just 8 weeks of NMES therapy plus progressive exercise. This suggests that NMES is relatively safe and well-tolerated, even in patients with significant chronic disease.

Both SPMS and PPMS are progressive diseases with inexorable decline, despite therapy.^{20,21} In the absence of acute relapses, the standard of care for SPMS and PPMS treatment is symptomatic only, recovery of lost functions is not expected, and the treatment goal is maintenance of function as long as possible.^{20–22} An earlier case report of an individual with SPMS¹⁰ who was treated with NMES and intensive nutrition related that this patient experienced marked gains in mobility over a period of 9 months. This case series also demonstrates that NMES coupled with progressive exercise

was well-tolerated and was associated with significant improvement in ambulation in patients with either SPMS- or PPMS-related gait disability.

For those patients with SPMS or PPMS muscle spasm, muscle pain, and disuse muscle atrophy—conditions which are often present along with MS-related gait disability—a referral to a physical therapist familiar with NMES for a trial of NMES may be beneficial. A prospective pilot of an interventional study of the use of NMES coupled with progressive exercise and intensive directed nutrition to ensure sufficient intake of nutrients critical for optimal brain metabolism in the setting of SPMS is underway.

Conclusions

Eight (8) of 9 patients with SPMS or PPMS experienced improvement in function as measured by EDSS scores and physical therapy assessment of gait. The 1 patient who did not have an improved EDSS score had received less than 30 days of NMES. All subjects reported NMES as being uncomfortable but tolerable. Only 1 patient elected to discontinue NMES in favor of switching to TENS for addressing neuropathic pain. To our knowledge, this article is the second report on using NMES-HEP to achieve functional gains in patients with SPMS successfully,¹⁰ and the first report on NMES-HEP achieving functional gains in patients with PPMS successfully.

Author Contributions

Dr. Wahls had full access to all the data in the case-series review and takes responsibility for the integrity of the data and accuracy of data analysis.

Drs. Reese and Kaplan were responsible for design concept and acquiring the data. Drs. Wahls, Reese, and Darling performed analysis and interpretation of the data. Drs. Kaplan and Wahls performed the statistical analysis. Drs. Wahls, Reese, and Darling drafted the manuscript for this article, and all three were responsible as well for critical revision of the manuscript for important intellectual content. Dr. Wahls also provided administrative, technical, and/or material support.

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Role of the sponsor

This is not applicable.

Disclosure Statement

Dr. Wahls reports that she owns the copyright to a book, titled, *Minding My Mitochondria*, which details the interventions used in the original case report of rehabilitation

T2 ▶

T3 ▶

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TABLE 3. PATIENT OUTCOMES

Pt	Days of NMES	Protocol	Function Prior to NMES	MMT	Outcome	Pre-NMES EDSS	Most recent EDSS	Δ EDSS
1	112	PP1/Foot switch	Roller walker, circumduction	MMT tibia anterioralis 3+/5, iliopsoas 4-/5, all others 4/5	Better heel strike, better endurance, no circumduction	5.5	5	0.5
2	62	PP1/PP6 spasm	1-2 canes, falls 1x/3weeks	MMT: LE 4-/5	Improved balance, using 1 cane to walk, < fall frequency ↓ 1 fall/M	6.5	6	0.5
3	116	PP1/Foot switch	Shuffling gait, foot drop, spasticity	MMT: LE 4+/5	Improved gait, better swing through, better heel strike, subjective report of better mood by patient	6.5	6	0.5
4	33	PP1/Δ to TENS setting	Slow walk, new pain in R hand	MMT: LE 4+/5, UE: 4+/5	Switched to TENS because pain was main disability	4.5	4	0.5
5	199	PP1/Foot switch	2 canes frequent falls	MMT: LE 3- to 4/5	Improved balance, improved endurance, no falls, can now jog 40 yards	4.5	3.5	1.0
6	495	PP1	AFO, 2 canes, scooter dependent	MMT: LE 3- to 4/5	Scooter no longer needed, walks easily without canes, bicycled 18 miles	6.5	4.5	2.0
7	106	PP1	Cane/scooter dependent	MMT: LE 4/5	Decreased spasm, better endurance but lost to follow-up	6.0	5.5	0.5
8	22	PP1	Roller walker/ marked spasms	MMT: LE 3 to 4/5	Lost to follow-up because of distance to treatment facility	6.5	6.5	0
9	112	PP1/Foot switch	1 cane frequent falls	MMT LE 3 to 4-/5	Better heel strike, better endurance, subjective reports of better mood by patient	6.0	5.5	0.5

Pt, patient; MNES, neuromuscular electrical stimulation; MMT, manual motor testing; EDSS, expanded Kurtzke Disability Status Scale; PP, preprogram; LE, lower extremity; TENS, transcutaneous electrical stimulation; UE, upper extremity; AFO.

of MS-related gait disability using intensive, directed nutrition, neuromuscular electrical stimulation and progressive exercise, has equity interest in a publishing company, TZ Press, L.L.C., and is a lecturer for the Kirkwood Community College and the New Pioneer Co-operative. The other authors (RD, KD, and DW) declare that they have no competing financial interests.

References

1. Daly JJ, Roenigk K, Holcomb J, et al. A randomized controlled trial of functional neuromuscular stimulation in chronic stroke subjects. *Stroke* 2006;37:172–178.
2. Yavuzer G, Geler-Kulcu D, Sonel-Tur B, et al. Neuromuscular electric stimulation effect on lower-extremity motor recovery and gait kinematics of patients with stroke: A randomized controlled trial. *Arch Phys Med Rehabil* 2006;87:536–540.
3. Carmick J. Clinical use of neuromuscular electrical stimulation for children with cerebral palsy, Part 1: Lower extremity. *Phys Ther* 1993;73:505–513.
4. Carmick J. Clinical use of neuromuscular electrical stimulation for children with cerebral palsy, Part 2: Upper extremity. *Phys Ther* 1993;73:514–522.
5. Neder JA, Sword D, Ward SA, et al. Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax* 2002;57:333–337.
6. Stein RB, Everaert DG, Thompson AK, et al. Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders. *Neurorehabil Neural Repair* 2010;24:152–167.
7. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: Health implications for the 21st century. *Am J Clin Nutr* 2005;81:341–354.
8. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: Update on dietary requirements for brain. Part 1: Micronutrients. *J Nutr Health Aging* 2006;10:377–385.
9. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: Update on dietary requirements for brain. Part 2: Macronutrients. *J Nutr Health Aging* 2006;10:386–399.
10. Reese D, Shivapour ET, Wahls TL, et al. Neuromuscular electrical stimulation and dietary interventions to reduce oxidative stress in a secondary progressive multiple sclerosis patient leads to marked gains in function: A case report. *Cases J* 2009;2:7601. AU3 ▶
11. Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *J Neurosci* 2001;21:5678–5684. ◀ AU4
12. Carro E, Trejo JL, Nunez A, Torres-Aleman I. Brain repair and neuroprotection by serum insulin-like growth factor I. *Mol Neurobiol* 2003;27:153162. ◀ AU5
13. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends Neurosci* 2007;30:464–472.
14. Longo FM, Yang T, Hamilton S, et al. Electromagnetic fields influence NGF activity and levels following sciatic nerve transection. *J Neurosci Res* 1999;55:230–237.
15. Radak Z, Toldy A, Szabo Z, et al. The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. *Neurochem Int* 2006;49:387–392.
16. Mechanisms and Management of Pain for the Physical Therapist. International Association for the Study of Pain, 2010. ◀ AU6
17. Quittan M, Sochor A, Wiesinger GF, et al. Strength improvement of knee extensor muscles in patients with chronic heart failure by neuromuscular electrical stimulation. *Artif Organs* 1999 May;23:432–435.
18. Quittan M, Wiesinger GF, Sturm B, et al. Improvement of thigh muscles by neuromuscular electrical stimulation in patients with refractory heart failure: A single-blind, randomized, controlled trial. *Am J Phys Med Rehabil* 2001;80:206–214.
19. Crevenna R, Marosi C, Schmidinger M, Fialka-Moser V. Neuromuscular electrical stimulation for a patient with metastatic lung cancer—a case report. *Support Care Cancer* 2006;14:970–973.
20. Tremlett H, Yinshan Z, Devonshire V. Natural history of secondary-progressive multiple sclerosis. *Mult Scler* 2008;14:314–324.
21. Ebers GC. Natural history of primary progressive multiple sclerosis. *Mult Scler* 2004;10(Suppl1):S8–S13.
22. Giovannoni G. Management of secondary-progressive multiple sclerosis. *CNS Drugs* 2004;18:653–669.

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APPENDIX. KURTZKE EXPANDED DISABILITY STATUS SCALE (EDSS) SCORE DEFINITIONS

Score	Definition
AU9 ▶ 0.0	Normal neurologic exam (all grade 0 in all Functional System [FS] scores)
1.0	No disability, minimal signs in one FS ^a (i.e., grade 1)
1.5	No disability, minimal signs in more than one FS ^a (more than 1 FS grade 1).
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2, or two FS grade 3 (others 0 or 1), or five grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding specifications for step 4.0)
5.5	Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities (usual FS equivalents are one grade 5 alone, others 0 or 1, or combination of lesser grades usually exceeding those for step 4.0)
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting (usual FS equivalents are combinations with more than two FS grade 3+)
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting (usual FS equivalents are combinations with more than two FS grade 3+)
7.0	Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; (usual FS equivalents are combinations with more than one FS grade 4+)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (usual FS equivalents are combinations, generally grade 4+ in several systems)
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (usual FS equivalents are combinations, generally 4+ in several systems)
9.0	Helpless bed patient; can communicate and eat; (usual FS equivalents are combinations, mostly grade 4+)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow; (usual FS equivalents are combinations, almost all grade 4+)
10.0	Death due to multiple sclerosis

^aExcludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in FS scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Note 3: The FSS and EDSS are ordinal clinical rating scales that are rated on the basis of the judgment of the examiner. Each of the FSS and the EDSS are single-item scales and there is no composite or summed score. The FSS include pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (or mental), and other.

Note 4: The FSS and EDSS are administered by a trained examiner.

Sources:

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* 1983;33:1444–1452.
Haber A, LaRocca NG, eds. *Minimal Record of Disability for Multiple Sclerosis*. New York: National Multiple Sclerosis Society, 1985.

AUTHOR QUERY FOR ACM-2010-0080-WAHLs_1P

AU1: Provide degrees for rest of authors.

AU2: There is no information about length of treatment or outcomes in Table 2; so we changed this mention to match what the tables actually show.

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