Effects of Physical Therapy and Dalfampridine on Function and Quality of Life in Nonambulatory Individuals With Multiple Sclerosis: A Randomized Controlled Trial

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ABSTRACT

BACKGROUND: Decreases in mobility, quality of life (QOL) and cognition are commonly seen in people with multiple sclerosis (MS). Physical therapy (PT) and exercise have been shown to improve many symptoms in ambulatory individuals with MS; however, evidence in nonambulatory people with MS is lacking. Dalfampridine is a US Food and Drug Administration-approved medication for MS that treats impaired ambulation by enhancing nerve conduction. To our knowledge, no study has examined the combined effect of PT and dalfampridine and very few studies have examined dalfampridine's effect on function in individuals with more progressive disease. The purpose of this study was to examine the effectiveness of PT combined with dalfampridine or a placebo on function, QOL, and cognition in nonambulatory individuals with MS. In addition, we explored the benefits of PT in all participants to increase the extremely limited research in this population.

METHODS: Adults with MS were randomly assigned to receive dalfampridine (n = 13) or placebo (n = 14) for 12 weeks in conjunction with PT treatment 2 times a week. Function, QOL, and cognition were assessed at baseline, 6 weeks, and 12 weeks.

RESULTS: There was a significant time × group interaction for the Multiple Sclerosis Quality of Life-54 favoring the placebo group. Both groups significantly improved on the 9-Hole Peg Test (left arm only), sitting lateral reach (right), transferring from wheelchair to mat, and repeated sit to stand.

CONCLUSIONS: The addition of dalfampridine to physical therapy did not improve function, QOL, or cognitive processing speed. Importantly, this study demonstrated an overall benefit in function and QOL with physical therapy 2 times a week for 12 weeks for nonambulatory individuals with MS.

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Multiple sclerosis (MS) presents in individual patients with a variety of clinical manifestations that can impact functional mobility. Substantial progress in treatment of the disease has significantly reduced relapse rates and improved disability outcomes. With the availability of more than 25 disease-modifying therapies time to walking limitation can be delayed for up to 20 years[1] and life expectancy has steadily increased.[2] Nevertheless, a sizable number of patients, especially those with progressive subtypes, advance to nonambulatory status.

Preserving mobility is consistently ranked as the most important factor impacting quality of life (QOL) in people with MS regardless of disability level or disease duration.[3] A strong correlation exists between impaired mobility and the capacity to live independently, complete activities of daily living (ADL), and participate in individual and community-based life roles.[4] These limitations can severely decrease QOL in people with MS.[5]

Another concerning and prevalent symptom of MS is cognitive impairment. It is estimated that 34% to 65% of people with MS are affected by cognitive decline; individuals with progressive forms of the disease fall toward the higher end of that range.[6,7] Research suggests that cognitive processing speed, memory, and learning are the faculties most impacted by the MS disease process.[7] Slow worsening on the Symbol Digit Modalities Test (SDMT) has been correlated with a decline in cognitive processing and gray matter volume loss due to neurodegeneration.[8,9]

Physical therapy (PT) and general exercise are well established interventions to preserve mobility and improve QOL in ambulatory individuals with MS.[10] In addition, cognitive changes, common in MS, may be impacted by exercise, although more studies are needed to draw definite conclusions. Evidence suggests that physically fit individuals with MS have less gray matter atrophy and, as a result, better cognitive function than their counterparts with MS who are less physically

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fit.[11] Growing evidence from both mouse and human studies shows that exercise impacts the central nervous system by decreasing neuroinflammation and improving both neuroprotection and axonal health.[12] Although the research has strengthened the efficacy of exercise in MS, the biggest knowledge gap that remains is to discern how exercise can impact the more progressive forms of the disease.[13]

Dalfampridine (also known as fampridine, 4-aminopyridine, 4-AP) is a broad-spectrum potassium channel blocker that has been shown to improve nerve conduction in demyelinated axons.[14] This oral medication binds to open potassium channels and delays repolarization of the nerve cell, extending the duration of the action potential and improving the strength of the nerve signal.[15] It has been demonstrated that 9 weeks of dalfampridine treatment results in a significant increase in walking speed as demonstrated by the timed 25-foot walk test in a subset of people with MS.[16]

Because of dalfampridine's mechanism of action, it is reasonable to hypothesize that the drug may impact other bodily functions besides ambulation and could improve functional mobility in people who are not ambulatory. In a small pilot study, 10 mg of dalfampridine given twice a day for 4 weeks was shown to improve upper extremity function in people with MS with an average Expanded Disability Status Scale (EDSS) score of 7.[4] The impact of dalfampridine on cognition, with an emphasis on processing speed, fatigue, and depression, has also been explored in a small number of studies with some promising results.[17-19]

To our knowledge, pairing exercise with dalfampridine treatment has not been explored. Because exercise has neuroprotective qualities and impacts the neuroplasticity of the central nervous system, it is rational to believe there may be potential for an augmented effect if the 2 were combined.

This randomized controlled trial examined the effectiveness of dalfampridine on function, QOL, and cognition in nonambulatory people with MS when it was administered in conjunction with 12 weeks of PT compared to a control group that received PT and a placebo. In addition, a secondary analysis to examine the benefits of PT in all participants was conducted to increase the extremely limited research in this population.

METHODS

Participants and Study Design

Participants were enrolled consecutively from a tertiary MS care center in Western New York State. Participants were included if they met the following criteria: (1) aged 20 years or older; (2) confirmed MS diagnosis[20] with an EDSS of 7.0 or higher[21]; (3) no steroid treatment in the last 30 days or a relapse in the last 90 days; (4) MS considered stable; and (5) capable of performing requirements of PT treatment, including at least a 2 of 5 score on the manual muscle test in 50% or more of the major muscle groups. Exclusion criteria were (1) history of seizure disorder; (2) major cognitive or mental illness that prevented ability to provide consent; (3) evidence of another medical cause of cognitive impairment besides MS; and (4) severe joint contractures that limited the ability to move within full active range of motion.

A double-blind, placebo-controlled randomized design was utilized comparing the PT intervention provided 2 times a week for 12 weeks in addition to either 10 mg of dalfampridine or placebo administered twice daily. Participants were randomly assigned in a 1 to 1 ratio to either treatment or placebo, and both the examiner and the physical therapist carrying out the treatments were blinded to the allocation. All participants provided written informed consent and the study was approved by the University at Buffalo, State University of New York Institutional Review Board.

Assessments

Once eligibility was confirmed and group assignment was complete, the participants underwent outcome measure testing at 4 different time points: twice, 2 weeks apart, with the scores averaged for baseline measurement (PT was scheduled to begin within 1 week after the second measure); at 6 weeks after initiation of PT; and at 12 weeks after completion of PT.

Every testing visit included the primary and secondary outcome measures, as described in the following sections.

Primary

The Five Times Sit to Stand Test (5XSTS) was performed 2 times with an interval of 2 minutes of rest between trials and was modified to allow participants to push off of the armrests and steady themselves when upright.[22] Using a stopwatch, the time was recorded to the nearest tenth of a second. The average of the 2 times was used for analysis.

Two summary scores (physical health and mental health) and 2 subscales of interest (energy/fatigue and overall) were calculated from the Multiple Sclerosis Quality of Life-54 (MSQOL-54).[23]

Secondary

To assess cognitive processing speed, the SDMT presents a key of numbers paired with abstract symbols at the top of a page. Participants are asked to fill in the correct numbers on a blank row of symbols using the key. At the conclusion of 90 seconds, the examiner counts the number of correct matches.[24]

Participants performed the 9-Hole Peg Test (9-HPT) 4 times, twice with the right hand, then 2 more trials with the left hand. The average of the trials for each hand was used for analysis.[25]

Performance of transfer (moving from one surface to another) is an item in the Functional Independence Measure used to objectively quantify (scoring from 1 "total dependency" to 7 "complete independence") an individual's ability to move from a wheelchair to a low mat table and from a low mat table back to a wheelchair.[26] This was measured once at each testing point.

Seated functional reach, measured in inches (forward and laterally), was tested in 3 trials. The number of inches reached in the 3 tests were averaged, and that result was used for analysis.[27]

Standardized performance scales for static standing have not been published. For this study, the examiner asked the patient to stand up using 2 hands on the parallel bars with the examiner guarding as needed. Once the participant stood upright, the examiner started the stopwatch. The time was stopped when the participant was unable to maintain an upright posture, which was defined as a flexing of the hips and

TABLE 1. Quality of Life and Cognition

	Drug group			Placebo group			*P* value		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks			
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Time	Drug	Time*Drug
PH	56.0 ± 24.4	54.6 ± 29.4	49.6 ± 24.8	48.9 ± 22.6[a]	59.3 ± 22.9[b]	59.9 ± 23.1[b]	.27	.78	**.01**
EM	60.9 ± 21.3	58.3 ± 27.5	55.6 ± 24.9	56.9 ± 20.4[a]	66.4 ± 16.2[b]	64.8 ± 18.8[b]	.44	.58	**.04**
FE	35.0 ± 18.5	34.3 ± 22.1	31.7 ± 25.2	28.4 ± 17.5	40.0 ± 21.9	40.1 ± 22.3	.32	.73	.11
Overall	57.9 ± 25.5[a]	59.5 ± 25.5[b]	54.1 ± 23.6[a]	48.5 ± 20.4[a]	67.0 ± 15.5[b]	63.4 ± 16.5[a]	**.01**	.75	**< .001**
SDMT	38.9 ± 13.3	40.2 ± 14.2	40.3 ± 14.9	**40.7 ± 10.1**	**42.8 ± 11.1**	42.0 ± 10.9	.06	.67	.84

EM, emotional health subscale of MSQOL-54; FE, fatigue/energy subscale of MSQOL-54; MSQOL-54, Multiple Sclerosis Quality of Life Scale-54; Overall, overall subscale of MSQOL-54; PH physical health subscale of MSQOL-54; SDMT, Symbol Digits Modality Test.

[a], [b] Post hoc analysis. Superscript a means are significantly different ($P < .05$) from superscript b means; however, all entries marked with [a] are not significantly ($P > .05$) different from each other and the same is true for all entries marked with [b].

Note: Increased score MSQOL-54 equates to improved QOL. Increased SDMT score equates to improved performance; score is number of items correctly matched.Bold equals statistical significance.

knees or bending the trunk forward more than 75°. Two trials were performed (separated by a 2-minute rest).The average of the 2 times was used for analysis.

PT Treatment

After the second baseline measurements, all participants were scheduled for their PT appointments within 1 week. The PT program consisted of 45-minute sessions 2 times a week for 12 weeks. The intervention was carried out by a blinded, licensed physical therapist who provided assistance and facilitation as needed. Progression of each exercise was based off the neurodevelopmental sequence to encourage functional movement. A home exercise program (HEP) was prescribed 3 times a week. The detailed exercises performed in each session and in the HEP are documented in **TABLE S1**.

Statistical Analysis

Using normative data for the main outcome measure,[28,29] a .08 power calculation with α .05 resulted in 17 participants in each group. All data is reported as means plus or minus SD, as analyzed by SPSS software (IBM Corp). A *t* test was utilized for demographic differences between groups. A mixed-factor repeated measures analysis of variance was used to evaluate within subject factor of time (baseline; 6 weeks; 12 weeks) and between subject factors of group (dalfampridine vs placebo). Data was checked for normal distribution and for equality of multiple variances utilizing the Box M test. When data was found to be nonparametric, a Friedman test was employed to determine significance. A *P* value < .05 was used to determine statistical significance for all tests. However, because of the exploratory nature of our study, if interactions had a *P* value < .08, a post hoc analysis of time points was examined.

RESULTS

A total of 35 people were recruited to the study with 29 completing the 3 testing time points. Six participants were lost throughout the project; 2 due to medical reasons and 4 to caregiver issues (completing ADL in time for transportation to pick up participant, absence of caregiver, caregiver unable to assist participant to transport van). Two additional participants were dropped from analysis because they completed less than half of the required PT treatments. Therefore, 27 participants were analyzed (13 on dalfampridine; 14 on placebo), with an average EDSS of 7.35 and a male-to-female ratio of 8:19. There were no significant demographic baseline features (**TABLE S2**) and no significant differences in baseline outcome measures between the groups.

Adherence to PT Treatment

Both groups were scheduled to participate in PT 2 times per week and perform an HEP 3 times per week, monitored weekly by the physical therapist. Of the 27 participants who completed the study, 82% attended more than 80% of the treatment sessions and the remaining 18% completed more than 70% of the sessions. Although difficult to truly assess, several of the participants reported impediments to fully adhering to the HEP. Most often the barrier to completion was a lack of caregiver assistance to safely perform the HEP.

QOL Measures

There was a significant time × group interaction for both the physical health and mental health summary scores on the MSQOL-54 (**TABLE 1**). The placebo group demonstrated significant improvements in QOL after 6 weeks and after 12 weeks of intervention, with the greatest increase in the first 6 weeks of treatment. In contrast, the dalfampridine group tended toward a decrease in QOL during treatment although it did not reach statistical significance. The overall QOL subscale includes 2 questions ("Overall, how would you rate your own quality-of-life?" rated on a visual analog scale of 0 [worst] to 10 [best] and "Which describes how you feel about your life as a whole?" with options from 1 "terrible" to 7 "delighted"). For both groups, scores on this subscale improved significantly after 6 weeks of treatment, however the significance was lost after 12 weeks. In addition, the placebo group demonstrated a greater improvement over time than the group receiving dalfampridine.

Cognitive Processing Speed

Although no significance was reached ($P = .06$), both groups tended toward improvement on the SDMT (**TABLE 1**). The

TABLE 2. Functional Status

	Drug group			Placebo group			*P* value		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks	Analysis of variance		
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Time	Group	Time*Group
Reaching (A)	12.2 ± 3.4	12.9 ± 3.9	12.2 ± 2.4	14.5 ± 3.7	14.4 ± 4.9	14.8 ± 4.5	.86	.14	.51
Reaching (R)	7.6 ± 3.0[a]	8.6 ± 3.3[b]	8.2 ± 2.3[b]	9.1 ± 3.8[a]	9.7 ± 4.2[b]	10.7 ± 3.9[b]	.02	.19	.18
Reaching (L)	7.4 ± 2.9	7.2 ± 2.1	6.9 ± 2.0	9.2 ± 3.4	9.5 ± 3.9	10.5 ± 3.8	.47*	.03	.18
9-HPT (R)	46.6 ± 23.3	43.3 ± 18.7	47.6 ± 22.3	37.8 ± 16.7	34.6 ± 13.5	37.0 ± 14.9	.12*	.20	.89
9-HPT (L)	49.1 ± 32.7[a]	47.5 ± 31.7[b]	43.8 ± 23.9[b]	45.0 ± 23.4[a]	45.0 ± 26.5[b]	39.9 ± 19.8[b]	.03*	.74	.84
W/C->Mat	5.2 ± 1.4	5.3 ± 1.2	5.6 ± 0.8	5.8 ± 0.9	5.6 ± 1.3	6.1 ± 0.5	.04	.21	.73
Mat -> W/C	5.2 ± 1.3	5.5 ± 1.1	5.3 ± 1.4	5.5 ± 1.2[a]	5.4 ± 1.2[a]	5.6 ± 1.2[b]	.25	.69	.05
5xSTS (s)	43.5 ± 60.2[a]	32.5 ± 44.9[b]	27.7 ± 22.9[b]	21.3 ± 6.8[a]	17.8 ± 5.6[b]	17.7 ± 6.1[b]	.004*	.18	.30
Standing (s)	108.6 ± 20.3	111.1 ± 21.7	114.3 ± 15.2	105.1 ± 23.8	106.2 ± 23.7	109.8 ± 24.0	.18*	.56	.95

* x^2 Friedman test

[a], [b] Post hoc analysis. Superscript a means are significantly different ($P < .05$) from superscript b means; however, all entries marked with [a] are not significantly ($P > .05$) different from each other and the same is true for all entries marked with [b].

5XSTS: 5 times sit to stand in seconds; decreased time equates to improved performance.

9-HPT, 9-Hole Peg Test right (R) and left (L) in seconds; decreased time equates to improved performance.

Reaching: Functional reach (inches); anterior (A); lateral to the left (L), and lateral to the right (R); increased distance equates to improved performance.

Standing: standing tolerance in seconds; increased time equates to improved performance.

W/C -> Mat: Transfer from wheelchair (W/C) to low mat. Mat -> W/C: Transfer from low mat to wheelchair; grading with the Functional Independence Measure. Increased score equates to improved performance.

dalfampridine group demonstrated a 1.4-point improvement, while the placebo group achieved a 2.1-point improvement. Secondary to the borderline *P* value, an exploratory post hoc was performed on each time point and a significant difference ($P = .04$) was found in the placebo group between the baseline and 6 week testing points.

Function

The functional results are summarized in **TABLE 2**.

9-HPT

There was a significant improvement on the 9-HPT in the left arm in both groups. Both groups demonstrated approximately a 5-second faster time to task completion throughout the 3 time points. This result was not seen in the right arm.

Transfers

There was a significant improvement in both groups from baseline to both the 6-week and 12- week time points when transferring from wheelchair to the low mat. The return transfer from the low mat to the wheelchair reached statistical significance at the final 12-week testing in the placebo group only.

Seated Functional Reach

No improvements were seen in either group during the anterior functional reach. However, statistical significance was reported for reaching to the right after both 6 weeks and 12 weeks of therapy.

Sit to Stand

Both groups improved their sit-to-stand times significantly. The group who took dalfampridine improved by 15.8 seconds while the placebo group improved by 3.6 seconds.

Standing Tolerance

Although no statistically significant differences were seen, there was a trend toward increased standing time in both the drug and placebo groups (5.7 and 4.7 seconds, respectively).

DISCUSSION

The purpose of this study was to evaluate whether nonambulatory individuals with MS would benefit from dalfampridine and PT versus placebo and PT. The dalfampridine group did not demonstrate improvement over the placebo group with any outcomes, however, the overall cohort demonstrated enhancements in functional mobility, cognitive processing, and QOL with PT 2 times a week for 12 weeks. This finding is important, as there are limited studies that show the benefit of PT for nonambulatory people with MS.

A 2017 systematic review identified the need for evidence about exercise in people with MS with moderate-severe disease, with only 19 articles in the final review. Most of these 19 studies had extremely low recruitment numbers with an average of 15 participants; the larger studies included EDSS scores as low as 3.0. Modes of exercise that have been studied in this population include conventional aerobic and resistive training; supported body weight treadmill training; and electric-stimulation–assisted cycling with less evidence in conventional therapy than in the more elaborate modalities.

We were able to recruit 35 people and a total of 27 participants were able to complete the entire protocol. This number of individuals with high EDDS scores is well above the average of other studies. The study budget provided transportation to and from the clinic. We feel that providing transportation increased interest in participation and facilitated better adherence to the regimen once participants were enrolled. However,

PRACTICE POINTS

Physical therapy 2 times a week for 45 minutes had a positive impact on quality of life and function in nonambulatory individuals with multiple sclerosis.

Continued access to rehabilitation should be an essential part of care plans for individuals with more severe forms of multiple sclerosis. ■

even with this accommodation, there were barriers to adherence. Due to legal obligations, our transportation company could not help clients out of their homes. Consequently, anyone who could not negotiate 1 step was unable to participate. In addition, participants who could not complete ADL and did not have a caregiver to assist were unable to get ready to travel.

Adherence to the dalfampridine schedule was established with continued monitoring at each PT visit and confirmed by caregivers, when possible. Common adverse effects of dalfampridine include difficulty sleeping, dizziness, nausea, headache, and increased pain. In our cohort, dalfampridine was well tolerated; no adverse effects were noted and there were no serious adverse events reported during the entirety of the study protocol.

Significant differences between the dalfampridine and placebo groups were only seen in 2 outcome measures (functional reach to the left and transferring from low mat to wheelchair), both favoring the placebo group. We attribute this to the small sample size, which was not adequate to perform a proper comparison. In addition, even though EDSS score differences were not statistically significant between groups, and our group comparison showed no statistical significance between outcome measures at baseline, the placebo group appeared to have better functional scores than the group taking dalfampridine. Interestingly, even though the placebo group had a seemingly higher functional status, their QOL measurements were lower at baseline than the dalfampridine group. Their lower QOL improved significantly over the dalfampridine group by the 6-week mark and remained higher at the 12-week measurement. It is unclear why the dalfampridine group's QOL measures trended downward throughout the study compared to the placebo group. However, the dalfampridine group's lower function may have resulted in more inconsistency in their symptoms. Throughout the testing procedures, we tried to mitigate the known variability and unpredictability of MS symptoms by averaging multiple trials of the same outcome.

When combining groups, there were significant improvements in 5 outcome measures (overall QOL subscale, functional reaching to the right, 9-HPT on the left hand, transferring from wheelchair to the low mat and back, and 5XSTS). To our knowledge, there is no study that has determined the minimal clinically important difference (MCID) of functional outcome measures in nonambulatory people with MS. The MCIDs of some of the same outcome measures were established in a similar study that examined the effects of slow release fampridine on arm and lower body function in ambulatory people with MS.[30] The researchers concluded that the MCID of the 9-HPT was 15.3% (0-15.3) and the 5XSTS was 34.6% (16.9-34.6). In addition to the aforementioned study, the MCID of the 5XSTS has been explored in vestibular disorders with a change of greater than or equal to 2.3 seconds being the threshold for clinical significance[29]; Møller et al reported a change of 25.5% to be a minimal reliable change in people with MS.[31] During our study, the percentage change of the 5XSTS from baseline to 12 weeks was 30%. The change in the dalfampridine group, who began with a poorer time, was 36% (43.45 seconds at baseline to 27.69 seconds at 12 weeks), surpassing the MCID, and the change in the placebo group was 17% (21.30 seconds to 17.68 seconds). The change of the 9-HPT for the left hand in our cohort was 11.1% (46.91 seconds to 41.70 seconds) by the end of the 12-week intervention. We hypothesize that the significant change in only the left was due to the left having more variance and limitation than the right which allowed for an increased opportunity for improvement. The minimal detectable change (MDC) for the lateral functional reach has been established in patients who experienced stroke at 2.3 cm to 2.67 cm.[32] Our lateral reach to the right improvement was 2.82 cm, which would surpass the requirement set for MDC in patients with stroke. When reaching to the right, the trunk muscles on the left must eccentrically contract to control the movement, which is followed by a concentric movement to sit back upright. We believe that the improvement seen with the right lateral reach mostly reflects an increase in left (nondominant) trunk muscle control for reasons similar to the improvement seen in the 9-HPT on the left. Although Taheri et al found that a 1.5 (physical) and 2.5 (mental) point change was enough to be considered clinically significant in a population of 265 people with MS,[33] MCID cutoffs for QOL scales have been notoriously hard to quantify. Our changes on the MSQOL-54 were much greater than the Taheri MCID, but our sample size was much smaller, so we are cautious about drawing a definite conclusion.

We feel it is important to report qualitative improvements that were not captured in our quantitative analysis. At 6 weeks into the intervention, 1 participant reported the ability to sign checks, which she had not been able to do for the past 2 years. She was in the placebo group, but was benefiting from specific rehabilitation interventions and general exercise. A participant in the dalfampridine group was able to return to ambulating short distances with a 4-wheeled rolling walker after being physically unable to get out of a wheelchair for the previous

2 years. Ambulation was not assessed during this study and thus this impressive finding was not captured. Most participants reported that they enjoyed getting out of the house and attending therapy twice a week. Caregivers also reported improvement in transfer status and ability to complete ADL.

Future studies should be conducted with fewer intervention barriers, for example, a home therapy or inpatient rehabilitation program may be more beneficial for nonambulatory individuals. Outcome measures that can provide a better picture of overall functional status would be ideal, but, at this time, they have not been developed. Another area that may strengthen results would be assessing caregiver burden to assess the subject's functional deficits and/or improvements. With dalfampridine's possible mechanism of improving conduction of action potentials along axons, functional improvements in nonambulatory people with MS is conceivable. Future studies should be conducted to examine the benefits of rehabilitation and dalfampridine to improve functional mobility and QOL for individuals living with a greater level of disability.

CONCLUSIONS

There were very few statistically significant differences in function, QOL, or cognitive processing speed between 2 groups of nonambulatory people with MS who received dalfampridine or placebo 2 times a day in conjunction with PT. Importantly, this study demonstrated an overall benefit in function and QOL by engaging in PT 2 times a week for 12 weeks for people who are nonambulatory and who have moderate to severe MS. ■

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PREVIOUS PRESENTATION: Preliminary findings from this study were presented at the at the Consortium of Multiple Sclerosis Centers Annual Meeting; May 28-31, 2014; Dallas, Texas.

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