Dalfampridine Effects Beyond Walking Speed in Multiple Sclerosis

Results from the STEADY Study

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Background: *Dalfampridine extended release (ER) improves walking in people with multiple sclerosis (MS), as demonstrated by walking speed improvement. This exploratory study evaluated treatment effects of dalfampridine-ER on gait, balance, and walking through treatment withdrawal and reinitiation.*

Methods: *Dalfampridine-ER responders, based on Timed 25-Foot Walk (T25FW) assessment before study entry, were included in this open-label, three-period, single-center study. Period 1: on-drug evaluations performed at screening and 1 week after screening. Period 2: dalfampridine-ER withdrawal and off-drug evaluations (days 5 and 11). Period 3: dalfampridine-ER reinitiation/final on-drug evaluation (day 15). Primary outcome variables: NeuroCom composite scores for gait and balance; balance was evaluated if gait changes were significant. Secondary variables: individual NeuroCom scores, walking speed (T25FW) and distance (2-Minute Walk Test [2MWT]), and balance (Berg Balance Scale [BBS]).*

Results: *All 20 patients completed the study: mean age, 53.1 years; mean MS duration, 11.3 years; mean time taking dalfampridine-ER, 315.3 days. NeuroCom gait composite scores worsened during period 2 relative to period 1 and improved during period 3; the mean $\pm$ SD difference in gait composite scores on drug was 4.03 ± 1.51 points ($P = .015$). Balance composite scores did not change significantly. Improvements were observed for off-drug versus on-drug for T25FW (0.36 ft/sec, $P < .001$), 2MWT (25.4 ft, $P = .006$), and BBS (1.7 points, $P = .003$). Safety profile was consistent with previous studies.*

Conclusions: *Significant improvements in gait, walking speed, distance, and balance were demonstrated by dalfampridine-ER reinitiation after a 10-day withdrawal period. Int J MS Care. 2015;17: 275–283.*

Multiple sclerosis (MS) is the most common cause of nontraumatic disability in young adults in the United States.¹ Gait dysfunction is common in people with MS, and ambulatory limitations have been identified as the most concerning functional limitation of the disease^{2,3}; their profound effect on function and quality of life in patients with MS contributes to the economic and societal burdens

imposed by MS.^{4–7} In a survey of patients with MS, 41% reported walking difficulty and 54% loss of balance.⁸

In patients with MS, gait impairments may arise from deficits such as spasticity, weakness, decreased proprioception, ataxia, diminished motor control, visual disturbance, fatigue, and vestibulopathy.⁹ In addition to gait impairments, abnormalities in balance control in MS have been associated with decreased ability to maintain position, limited and slow movements toward limits of stability, and delayed responses to postural disturbances or perturbations.¹⁰

Dalfampridine is a voltage-dependent potassium channel blocker that has been shown to promote the restoration of action potential conduction in demyelinated axons in animal studies.¹¹ In the United States, dalfampridine extended release (ER) (Ampyra extended-release tablets; Acorda Therapeutics Inc, Ardsley, NY),

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DOI: 10.7224/1537-2073.2014-036

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in Europe, prolonged-release fampridine, and elsewhere, fampridine modified or sustained release, 10 mg twice daily, have been approved to improve walking in people with MS,¹² as demonstrated by an increase in walking speed in two phase 3 clinical trials.^{13,14} Several studies have shown that people with MS experience a range of gait abnormalities, including decreased step length, decreased cadence, reduced joint motion, and variability in other gait parameters, which can result in reduced gait speed.³ Based on the evidence that dalfampridine-ER improves walking, it was thought that the observed clinical benefit of dalfampridine-ER might be, in part, related to changes in gait and balance. Thus, an exploratory study was designed to assess for treatment effect on measures of gait and balance parameters in patients who had been receiving dalfampridine-ER as part of their regular MS clinical care and had shown improved walking speed.

Methods

Study Design

STEADY—the Effects of Dalfampridine-ER on Speed, Gait, Balance, and Distance Walked in Patients with MS Study—was a single-center, single-arm, open-label proof-of-concept trial of dalfampridine-ER 10 mg twice daily (Figure 1). The study consisted of three consecutive periods: period 1 was a 7-day on-drug screening phase, with evaluations performed on the initial day (visit 1) and 1 week later, on study day 1 (visit 2), at which time dalfampridine-ER treatment was withdrawn;

period 2 was a 10-day off-drug phase, with evaluations performed on day 5 (± 2 days) (visit 3) and day 11 (± 2 days) (visit 4), after which dalfampridine-ER treatment was reinitiated; and period 3 was a 4-day on-drug phase, with a final evaluation performed on day 15 (± 2 days) (visit 5). A withdrawal and reinitiation protocol was used because in the absence of a placebo group, such a study design can help determine whether observed effects are a direct result of treatment.

Study Patients

Twenty patients aged 20 to 65 years with a definite MS diagnosis by the revised McDonald criteria¹⁵ participated in this study between January 19 and May 3, 2012. For study inclusion, patients were required to have been using dalfampridine-ER 10 mg twice daily for at least 2 weeks before screening and to have been Timed 25-Foot Walk test (T25FW)¹⁶ responders, defined as showing improvement of at least 20% in walking speed between an off-drug and on-drug evaluation before study entry, as determined by a study investigator (GP, a board-certified neurologist specializing in MS care). The T25FW was administered per established clinical protocols.

The key exclusion criteria were history of seizures other than simple febrile seizures; history or presence of moderate or severe renal impairment, defined by a calculated creatinine clearance of 50 mL/min or less estimated using the Cockcroft-Gault equation; or history of urinary tract infection within 4 weeks of screening.

Throughout the study, non-study-drug medications, including MS disease-modifying and symptomatic therapies, were permitted provided that the patient had been receiving a stable regimen for at least 4 weeks before screening.

The study received approval from the institutional review board of the Oklahoma Medical Research Foundation, Oklahoma City, OK, and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation for Good Clinical Practices. Before all study procedures, written informed consent was obtained from all patients.

Outcome Variables

At each visit, multiple gait and balance variables were measured using the NeuroCom system, which has previously

demonstrated utility for evaluating gait and balance in MS¹⁷ and across a variety of other diseases.¹⁸⁻²¹ The study used the SMART Balance Master (NeuroCom, a division of Natus, Clackamas, OR), a device equipped with a movable visual surround and a dual-plate force platform with rotation capabilities to measure the vertical forces exerted by the patient's feet on the force plate for assessment of balance. The NeuroCom long force plate was also used, which is a walking platform for the assessment of gait parameters by measuring vertical forces to determine center of gravity position and postural control during ambulation. The device provides objective assessments and retraining of the sensory and voluntary motor control of balance and visual feedback on either a stable or unstable support surface in a stable or dynamic visual environment. For this study, protocols that closely reflect daily activities were selected; hence, evaluations representing steady-state ambulation, direction change, adaptation to surface irregularities, reaching, and integration of sensory inputs were chosen.

The following tests were used to evaluate gait variables: the Walk Across test to measure step width, step length, speed, and step length symmetry; the Tandem Walk test to measure step width, speed, and endpoint sway velocity; and the Step/Quick Turn test to measure the turn time and turn sway. Balance was evaluated using the following tests: the Sensory Organization test to assess the use of visual, proprioceptive, and vestibular cues on postural stability; the Adaptation test to assess the patient's ability to minimize sway when exposed to irregular surfaces and inclinations (toes up or toes down directional rotations were performed to induce postural instability); and the Limits of Stability test to assess the maximum distance that the patient can displace the center of gravity without losing balance, stepping, or reaching for assistance.

Statistical Analyses

Primary Outcomes and Analyses

Given that this was an exploratory study, two previously unreported measures were used as primary outcome variables: an overall gait score derived using NeuroCom gait domains (Walk Across, Tandem Walk, and Step/Quick Turn) and an overall balance score from three balance domains (Sensory Organization, Adaptation, and Limits of Stability). Each score was derived by a four-step procedure:

1. To standardize the raw data, each individual test score in a NeuroCom domain (eg, a patient's walking speed score in the Walk Across domain)

was converted to a z score based on the mean and standard deviation for the data from visit 1. If a test was designed to have multiple trials, the trial findings were averaged, and for tests in which lower scores represented better performance, the z score was multiplied by -1 so that for all tests, higher scores would signify improvement.

2. The z scores were averaged, creating a domain score. For example, a patient's step width, step length, step length symmetry, and walking speed z scores were averaged, yielding a Walk Across score.
3. The domain scores were averaged, yielding an overall score. For gait, overall score was the unweighted average of Walk Across, Tandem Walk, and Step/Quick Turn scores. For balance, overall score was the weighted average of Sensory Organization (0.5), Adaptation (0.2), and Limits of Stability (0.3) scores based on the representation of each task on ambulatory activities in regular daily life.
4. To facilitate interpretation, each overall score was converted to a percentile using the standard normal distribution.

The primary analysis evaluated the overall composite gait and balance scores by treatment, comparing on drug (periods 1 and 3) versus off drug (period 2). This analysis was performed using a repeated-measures mixed-model analysis of variance with a fixed effect for treatment. Visit was included as a repeated statement in the statistical analysis program to account for inpatient correlation between time points. Statistical significance was defined as $\alpha < .05$, and to maintain this alpha level, overall composite balance was tested only if the gait outcome was significant.

Differences in overall gait and balance scores were also compared between individual study periods as a secondary prespecified analysis using a mixed-model analysis of variance with pairwise comparisons adjusted by the Tukey honestly significant difference test. Comparisons were of period 1 (dalfampridine-ER) versus period 2 (dalfampridine-ER withdrawn); period 3 (dalfampridine-ER reinitiated) versus period 2 (dalfampridine-ER withdrawn); and period 3 (dalfampridine-ER reinitiated) versus period 1 (dalfampridine-ER).

The summary of results is presented as least squares (LS) means, with P values comparing the difference in LS means.

Secondary Outcomes and Analyses

Secondary outcomes included the individual NeuroCom tests in each domain, as well as non-NeuroCom

variables for gait and balance measured at each visit. For gait, the non-NeuroCom variables included walking speed and walking distance, assessed using the T25FW and the 2-Minute Walk Test (2MWT),²² respectively, and balance, assessed using the Berg Balance Scale (BBS).²³ Changes in secondary outcome variables were evaluated using the same methods as for the primary variables. Because these secondary variables were exploratory, correction for multiple comparisons was not performed. Correlation between overall scores, for gait and balance, with each of the non-NeuroCom measures was tested by calculation of a Pearson correlation coefficient.

All computations were performed using SAS software, version 9 (SAS Institute Inc, Cary, NC).

Tolerability

The safety and tolerability of dalfampridine-ER treatment were assessed by reviewing treatment-emergent adverse events (TEAEs) and changes from baseline in vital signs. A TEAE, which was defined as an adverse event with onset or worsening that occurred on or after the screening visit through 30 days after the last dose taken in period 3, was evaluated across the three study periods. Adverse events were summarized by treatment at the time of event, and clinically significant changes were counted and tabulated.

Results

Patients

All 20 patients completed the study. Baseline demographic and clinical characteristics (Table 1) show that the population was mainly women (60%) and predominantly white (90%). The mean age of study participants was 53.1 years, and the mean duration of MS was 11.3 years. The most common MS type was relapsing-remitting disease (65%), and the mean duration of dalfampridine-ER use before study entry was 315.3 days.

Primary Outcome: NeuroCom Composite Scores

Gait

By treatment, the mean overall gait score was significantly higher on drug (periods 1 and 3) than off drug (period 2) (Figure 2A), with a difference in LS means of 4.03 percentile points ($P = .015$). By study period (Figure 2B), the score was lower, with an LS mean difference of 3.31 points, after dalfampridine-ER withdrawal (period 2 vs. period 1); however, the difference was not significant ($P = .124$). Dalfampridine-ER reinitiation increased overall gait score, with a significant difference in LS means of 6.48 points ($P = .032$, period 3 vs.

Table 1. Baseline demographic and clinical characteristics of the 20 study patients

Characteristic	Value
Sex, No. (%)	
Female	12 (60)
Male	8 (40)
Age, y	
Mean $\pm$ SD	53.1 $\pm$ 11.0
Median (range)	56.5 (20–65)
Race, No. (%)	
White	18 (90)
Black	1 (5)
Other	1 (5)
MS diagnosis, No. (%)	
Relapsing-remitting	13 (65)
Secondary progressive	3 (15)
Primary progressive	2 (10)
Progressive relapsing	2 (10)
MS duration, y	
Mean $\pm$ SD	11.3 $\pm$ 8.4
Median (range)	7.8 (3–29)
Disease-modifying therapy, No. (%)	
Glatiramer acetate	8 (40)
Interferon β -1a	3 (15)
Interferon β -1b	3 (15)
Natalizumab	2 (10)
Fingolimod	1 (5)
None	3 (15)
Dalfampridine-ER treatment duration before study enrollment, d	
Mean $\pm$ SD	315.3 $\pm$ 270.5
Median (range)	355.5 (14–685)
Berg Balance Scale score ^a	
Mean $\pm$ SD	47.4 $\pm$ 7.0
Median (range)	48.5 (32–56)

Abbreviations: ER, extended release; MS, multiple sclerosis.

^aAt visit 1, on drug.

period 2); the LS mean difference between period 3 and period 1, 3.17 points, was not significant ($P = .380$).

Balance

Because the mean overall gait score was significantly higher on drug than off drug (see previously herein), analysis of balance was warranted per the multiple comparisons testing procedure. Mean overall balance scores are displayed in Figure 2C and Figure 2D. By treatment (Figure 2C), no drug effect was observed (LS mean difference, on drug vs. off drug: -2.38 percentile points, $P = .434$). By study period (Figure 2D), however, progressive improvement was observed. The improvement after dalfampridine-ER withdrawal (ie, from period 1 to period 2) was not significant (LS mean difference: 6.48 points, $P = .114$). In contrast, the improvement after dalfampridine-ER reinitiation was significant relative to withdrawal (LS mean difference, period 3 vs. period

turn sway ($P = .029$ and $P = .043$, respectively), but not for turn time.

For balance, Sensory Organization test scores were not significantly higher on drug than off drug, although patients performed better over time, including a significantly higher mean score after dalfampridine-ER reinitiation than during withdrawal (period 3 vs. period 2, $P = .003$). Adaptation test scores did not show a treatment effect. However, for the toes-up score, there was a significant difference when comparing the off-drug versus the on-drug period that favored the off-drug period ($P = .010$); no significant differences were observed for the toes-down score. Limits of Stability test scores were significantly higher on drug than off drug for movement velocity ($P = .003$). Although movement velocity was significantly higher after dalfampridine-ER reinitiation than during the off-drug period (period 3 vs. period 2, $P = .003$), the value during dalfampridine-ER withdrawal was numerically higher than the initial on-drug value.

Non-NeuroCom Variables

Walking

By treatment (Figure 3A), walking speed, assessed using the T25FW, was significantly faster on drug than off drug, by a difference in LS means of 0.36 ft/sec ($P < .001$). By study period (Figure 3B), period 2 (dalfampridine-

ER withdrawal) was associated with a significant deterioration in walking speed relative to period 1, by a difference in LS means of 0.38 ft/sec ($P < .001$). Reinitiation of dalfampridine-ER (period 3) resulted in significant improvement relative to period 2, by a difference in LS means of 0.42 ft/sec ($P = .006$), to a speed similar to that before dalfampridine-ER withdrawal (LS mean difference of 0.04 ft/sec relative to period 1, $P = .783$).

Comparison of mean 2MWT scores by treatment (Figure 3C) showed significantly greater walking distance on drug relative to off drug by a difference in LS means of 25.4 ft ($P = .006$). By study period (Figure 3D), period 2 was associated with a significantly shorter walking distance relative to period 1 (difference in LS

2: 10.66 points, $P = .029$) and also compared with the level before withdrawal (LS mean difference, period 3 vs. period 1: 17.14 points, $P < .001$).

Secondary Outcomes: NeuroCom Variables

The results of individual NeuroCom gait and balance tests are presented in Table 2. Briefly, for gait, Walk Across scores were significantly lower on drug than off drug for step width ($P = .032$) and significantly higher for step length ($P < .001$) and walking speed ($P < .001$), but not for step length symmetry. Tandem Walk scores were similar on drug and off drug; however, patients walked significantly faster in period 3 than in period 2 ($P = .028$). Step/Quick Turn scores were significantly lower on drug than off drug for both left turn and right

Table 2. Mean $\pm$ SD scores on individual NeuroCom gait and balance tests

Test	By treatment		By study period		
	Off drug	On drug	Period 1 (on drug)	Period 2 (dalfampridine- ER withdrawn)	Period 3 (dalfampridine- ER reinitiated)
NeuroCom gait tests					
Walk Across (n = 20)					
Step width, cm	20.5 $\pm$ 3.6	20.1 $\pm$ 3.6*	19.8 $\pm$ 3.9	20.5 $\pm$ 3.6	20.8 $\pm$ 3.9
Step length, cm	47.6 $\pm$ 17.0	55.4 $\pm$ 15.8***	55.7 $\pm$ 15.6***	47.6 $\pm$ 17.0	54.9 $\pm$ 18.9**
Speed, cm/sec	56.8 $\pm$ 22.5	64.5 $\pm$ 19.4***	64.6 $\pm$ 19.2***	56.8 $\pm$ 22.5	64.3 $\pm$ 21.8**
Step length symmetry, %	5.0 $\pm$ 27.8	1.8 $\pm$ 24.3	1.4 $\pm$ 26.9	5.0 $\pm$ 27.8	4.6 $\pm$ 26.0
Tandem Walk (n = 16)					
Step width, cm	14.1 $\pm$ 8.6	13.2 $\pm$ 5.6	13.0 $\pm$ 6.4	14.1 $\pm$ 8.6	13.6 $\pm$ 5.9
Speed, cm/sec	19.4 $\pm$ 10.3	21.2 $\pm$ 7.3	20.0 $\pm$ 8.2	19.4 $\pm$ 10.3	23.5 $\pm$ 7.5*
End sway, $^{\circ}$ /sec	7.2 $\pm$ 4.1	8.3 $\pm$ 3.0	8.2 $\pm$ 3.2	7.2 $\pm$ 4.1	8.1 $\pm$ 4.3
Step/Quick Turn (n = 20)					
Left turn time, sec	2.13 $\pm$ 1.43	1.85 $\pm$ 1.12	1.92 $\pm$ 1.17	2.13 $\pm$ 1.43	1.74 $\pm$ 1.17
Right turn time, sec	2.11 $\pm$ 1.40	1.83 $\pm$ 1.02	1.91 $\pm$ 1.06	2.11 $\pm$ 1.40	1.69 $\pm$ 1.14
Left turn sway, $^{\circ}$	35.8 $\pm$ 12.3	33.2 $\pm$ 11.6*	33.6 $\pm$ 11.4	35.8 $\pm$ 12.3	32.9 $\pm$ 14.1
Right turn sway, $^{\circ}$	36.2 $\pm$ 13.4	33.2 $\pm$ 10.8*	33.5 $\pm$ 11.5	36.2 $\pm$ 13.4	33.2 $\pm$ 13.8
NeuroCom balance tests					
Sensory Organization (n = 20)					
Equilibrium composite score	53.4 $\pm$ 20.2	54.5 $\pm$ 17.3	52.2 $\pm$ 16.8	53.4 $\pm$ 20.2	59.3 $\pm$ 20.0**
Adaptation (n = 20)					
Toes up score	67.2 $\pm$ 20.8 ^a	75.7 $\pm$ 25.4*	77.8 $\pm$ 28.8*	67.2 $\pm$ 20.8 ^a	71.6 $\pm$ 21.8
Toes down score	67.8 $\pm$ 28.8	69.8 $\pm$ 30.5	70.0 $\pm$ 32.3	67.8 $\pm$ 28.8	69.3 $\pm$ 31.5
Limits of Stability (n = 11–19)					
Reaction time, sec	0.96 $\pm$ 0.15 ^b	0.92 $\pm$ 0.18 ^a	0.94 $\pm$ 0.20 ^c	0.96 $\pm$ 0.15 ^b	0.90 $\pm$ 0.21 ^d
Movement velocity, $^{\circ}$ /sec	3.51 $\pm$ 1.03 ^b	3.59 $\pm$ 0.80*** ^a	3.34 $\pm$ 0.89 ^c	3.51 $\pm$ 1.03 ^b	3.65 $\pm$ 0.79*** ^d
Endpoint excursion, %	56.4 $\pm$ 18.5 ^b	56.6 $\pm$ 11.1 ^a	56.4 $\pm$ 11.8 ^c	56.4 $\pm$ 18.5 ^b	55.0 $\pm$ 10.7 ^d
Maximum excursion, %	74.0 $\pm$ 15.1 ^b	76.5 $\pm$ 11.4 ^a	74.6 $\pm$ 12.2 ^c	74.0 $\pm$ 15.1 ^b	74.7 $\pm$ 10.6 ^d
Directional control, %	66.6 $\pm$ 17.5 ^b	67.3 $\pm$ 12.5 ^a	68.1 $\pm$ 12.8 ^c	66.6 $\pm$ 17.5 ^b	66.2 $\pm$ 11.8 ^d

Abbreviation: ER, extended release.

* $P < .05$, ** $P < .01$, *** $P < .001$; comparisons reflect the column headings, ie, on drug vs. off drug, and period 1 vs. period 2 or period 3 vs. period 2.

^an = 19.

^bn = 14.

^cn = 17.

^dn = 11.

means of 25.7 ft, $P = .014$), and period 3 resulted in significant improvement relative to period 2 (difference in LS means of 37.1 ft, $P = .011$) to a distance similar to that during period 1 (LS mean difference of 11.4 ft relative to period 1, $P = .322$).

Balance

Comparison of BBS scores by treatment (Figure 3E) shows that scores significantly favored dalfampridine-ER, by an LS mean difference of 1.7 points ($P = .003$). By study period (Figure 3F), scores showed significant deterioration during dalfampridine-ER withdrawal (LS mean difference, period 2 vs. period 1: 1.5 points, $P = .040$) and significant improvement after dalfampridine-ER reinitiation (LS mean difference, period 3 vs. period 2: 2.0 points, $P = .018$).

Correlations Among Outcome Variables

Overall gait score was correlated with all three non-NeuroCom variables, with a Pearson correlation coefficient of 0.71 for the T25FW, 0.70 for the 2MWT, and 0.76 for the BBS. Although overall balance scores were also correlated with the non-NeuroCom variables, these correlations were not as strong, with correlation coefficients of 0.49, 0.46, and 0.51 for the T25FW, 2MWT, and BBS, respectively. All correlations were significant ($P < .001$).

Tolerability

The incidence of TEAEs is summarized in Table 3. Overall, six patients (30%) reported one or more TEAEs. None was serious, led to discontinuation, or was deemed by investigators to be treatment related. All

but one TEAE (a fall) were reported off drug, during period 2.

Discussion

In this study, patients who previously responded to dalfampridine-ER 10 mg twice daily used as part of their regular MS clinical care demonstrated improvement in overall gait as well as walking speed and distance after periods of dalfampridine-ER withdrawal and reinitiation. On 4 days of dalfampridine-ER reinitiation, after a withdrawal period of 10 days, patients exhibited a rapid, statistically significant mean improvement in overall gait, as quantified by an objective, computerized assessment using the NeuroCom SMART Balance Master and long force plate. This improvement is similar to that observed for walking speed during the transition from the double-blind phase of the dalfampridine-ER pivotal studies to the open-label extension.²⁴ Accordingly, the mean improvement in walking speed observed after 8 weeks of dalfampridine-ER treatment in dalfampridine-ER responders in the double-blind phase was lost after dalfampridine-ER discontinuation. Subsequent dalfampridine-ER reinitiation in the open-label extension phase improved walking speeds within 2 weeks to levels similar to those observed at the end of double-blind treatment. The quick loss of treatment effects, followed by the rapid improvement with dalfampridine-ER reinitiation, likely reflects the described pharmacokinetics of dalfampridine-ER²⁵ and its putative mechanism of action.²⁶ Nonetheless, the dalfampridine-ER pivotal trials did not examine the treatment effect on gait or balance parameters.

As stated in a consensus statement, a complete MS gait evaluation must include multiple aspects of gait parameters⁹; use of the NeuroCom system enabled the measure of several gait parameters, including step width, step length, speed, endpoint sway velocity,

Figure 3. Comparison of non-NeuroCom outcomes by treatment (A, C, and E) and period (B, D, and F)

A and B, Walking speed evaluated using the Timed 25-Foot Walk test. C and D, Walking distance evaluated using the 2-Minute Walk Test. E and F, Balance evaluated using the Berg Balance Scale (BBS). ER, extended release; LS, least squares.

Table 3. Treatment-emergent adverse events

Adverse event ^a	Incidence, No. (%)			
	Period 1	Period 2	Period 3	Total
Any	1 (5)	5 (25)	0	6 (30)
Fall	1 (5)	1 (5)	0	2 (10)
Fatigue	0	1 (5)	0	1 (5)
Gait disturbance	0	1 (5)	0	1 (5)
Hypertonia	0	1 (5)	0	1 (5)
Hypokinesia	0	1 (5)	0	1 (5)
Muscular weakness	0	1 (5)	0	1 (5)
Nausea	0	1 (5)	0	1 (5)
Presyncope	0	1 (5)	0	1 (5)
Vertigo	0	1 (5)	0	1 (5)
Vision blurred	0	1 (5)	0	1 (5)

^aBy Medical Dictionary for Regulatory Activities preferred term.

turn time, and turn sway. In the present exploratory study, statistically significant on-drug improvement was observed in several gait parameters, contributing to the overall score. The overall composite gait score showed high correlations with walking speed (T25FW) and distance (2MWT), as well as with balance assessed using the BBS. In contrast to gait, no statistically significant differences were observed for the on-drug versus off-drug periods for the NeuroCom overall balance score. However, the mean balance score showed a small but nonsignificant improvement on withdrawal of dalfampridine-ER that was also followed by additional improvement on dalfampridine-ER reinitiation. This trend in improvement on the balance assessments during the three periods suggests at least a partial learning effect, as has previously been described using NeuroCom assessments.¹⁸ In a study of healthy young adults performing a Sensory Organization test five times over 2 weeks, a learning effect was documented, with an apparent plateau at the third to fourth session and retention of the effect at a sixth session a month afterward.²⁷ In the present study with dalfampridine-ER withdrawal followed by reinitiation, the progressive improvement across the three periods, with a significant increase between periods 2 and 3, suggests a possible treatment effect beyond a learning effect. Further studies are needed to differentiate these effects.

For its part, the BBS, a 14-item physician-rated scale that rates balance performance based on a set of motor tasks, such as the ability to sit, stand, lean, turn, and posturally transition, identified statistically significant deterioration after dalfampridine-ER withdrawal and significant improvement on dalfampridine-ER reinitiation. Although the BBS is an effective and reliable tool to assess for balance abnormalities, the evaluations are

primarily of static balance and, therefore, do not provide information on dynamic functions.²⁸ The lack of significance on the overall balance composite score suggests that NeuroCom force platform devices, which use dynamic posturography, evaluate different aspects of balance relative to BBS. Nevertheless, the NeuroCom overall balance score showed moderate correlation with BBS score and with walking speed (T25FW) and distance (2MWT).

Walking is a complex task that requires the coordination of multiple functional domains, with contributions from strength and balance to proprioceptive, vestibular, and visual input. In MS, relapses or progression involving any of the neurologic systems may affect gait and balance in ways not captured by measuring solely walking speed. Thus, this study suggests that the improvement in walking speed observed with dalfampridine-ER may be explained, in part, by an effect on multiple domains of walking.

The tolerability profile of dalfampridine-ER was consistent with that of previous studies. Withdrawal of dalfampridine-ER for 10 days did not result in any clinically significant tolerability findings.

Given that this was an exploratory study to assess for potential treatment effect of dalfampridine-ER on gait and balance, the interpretation and generalizability of the results are subject to limitations, including the small sample size and the open-label and nonrandomized design, although the population did consist of dalfampridine-ER responders in actual clinical practice. In this regard, the broad age range (20–65 years) should also be noted as a potential limitation. Although such a wide range may be expected in an MS population treated with

PracticePoints

- Dalfampridine extended release (ER) is available (in the United States and elsewhere) to improve walking in people with MS as demonstrated by an improvement in walking speed.
- This exploratory study evaluated gait, balance, and walking changes in patients with MS identified as dalfampridine-ER responders based on walking speed through dalfampridine-ER withdrawal and reinitiation.
- Significant improvements in gait, walking speed, distance, and balance were demonstrated by dalfampridine-ER reinitiation after a 10-day withdrawal period.

dalfampridine-ER, it is possible that some of the study results (ie, lack of variability and statistical significance) may have resulted from the inclusion of older patients because gait and balance are affected by age-related factors in addition to the more direct effects of MS. In addition, the use of composite scores for NeuroCom gait and balance variables was novel, and, therefore, to interpret the clinical utility of these scores, further studies are warranted. Furthermore, as stated in the Methods section, comparisons for the secondary variables, including the non-NeuroCom measures and individual NeuroCom tests, were not protected for multiple comparisons and should be interpreted in this context. Finally, because this was an exploratory study, evaluation of all measures was based on statistical significance; therefore, interpretation of clinical significance must be in context and with caution.

In summary, the results of this study provide evidence that not only supports the benefits of dalfampridine-ER on walking, as demonstrated by improvements in speed and distance, but also expands these benefits to include parameters of gait and balance, the latter demonstrated by the BBS. Furthermore, the results of this study may be used for generating hypotheses regarding the effects of dalfampridine-ER on walking, considering that new measures were used to evaluate dalfampridine-ER and the drug seemed to improve several of these domains. These effects, which may be explained by observed improvements in specific gait and balance parameters, warrant further evaluation. □

Acknowledgments: Editorial assistance was provided by E. Jay Bienen, PhD, of The Curry Rockefeller Group LLC, Tarrytown, NY, and funded by Acorda Therapeutics, Inc, Ardsley, NY.

Financial Disclosures: Drs. Suárez and Henney were employees of and stockholders in Acorda Therapeutics Inc at the time of this study. Mr. Klingler and Dr. Rabinowicz are currently employees of and stockholders in Acorda Therapeutics Inc. Dr. Pardo has received personal compensation for speaking or consulting for Acorda Therapeutics Inc, Bayer, Biogen Idec, EMD Serono, Genzyme, Novartis, Pfizer, and Teva.

Funding/Support: This work was supported by Acorda Therapeutics Inc, Ardsley, NY.

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