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Effects of dalfampridine on multi-dimensional aspects of gait and dexterity in multiple sclerosis among timed walk responders and non-responders

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ABSTRACT

Background: Dalfampridine extended release 10 mg tablets (D-ER) have demonstrated improvement in walking for ambulatory persons with multiple sclerosis (pwMS), termed "responders."
Objective: This study examined the extent additional aspects of gait and dexterity change for patients prescribed D-ER.
Methods: Over 14-weeks, walking endurance, dynamic gait, self-report walking ability andfine and gross dexterity were examined in pwMS prescribed D-ER as a part of routine clinical care.
Results: The final results (n = 39) validate that a subset of pwMS improve walking speed (Time 25-Foot Walk Test, $p < 0.0001$). Significant improvements in gait and dexterity were observed even among participants who did not improve walking speed. Improvements were evident in gait and dexterity domains including Six Minute Walk Test, $p = 0.007$, Six-Spot Step Test, $p < 0.0001$, Multiple Sclerosis Walking Scale-12, $p < 0.0001$, Nine Hole Peg Test, $p < 0.0001$ dominant and non-dominant sides, and Box and Blocks Test, $p = 0.005$ and 0.002, dominant and non-dominant sides, respectively.
Conclusions: These findings suggest that D-ER may be a potential treatment for gait impairments, beyond walking speed and dexterity in pwMS. Further investigation regarding D-ER response is warranted.

1. Introduction

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that produces axonal damage and loss of myelin [1]. Loss of myelin leads to delayed or complete blockade of nerve impulse conduction [1,2]. Abnormal nerve conduction plays a significant role in how functional activities such as ambulation are completed in persons with MS (pwMS) [3,4]. In 2010, dalfampridine extended release 10 mg tablets (D-ER; Ampyra Extended Release Tablets, Acorda Therapeutics, Inc.) were approved by the Food and Drug Administration (FDA) for treatment to improve walking in pwMS as demonstrated by an increase in walking speed.

In the pivotal D-ER clinical trials, the primary outcome was walking speed using the Timed 25-Foot Walk Test (T25FW) [5–7]. Efficacy was based on consistency of walking speed improvement over repeated trials. Specifically, a "responder" was defined as an individual with a faster walking speed for at least three of the four on-drug visits compared to the maximum speed recorded during the five off-drug visits [5–7]. Using this "responder" definition, the two phase III clinical trials found 35%-43% of pwMS receiving D-ER had significant improvement in walking speed compared to 8-9% in the placebo groups [6,7].

Pharmacologically, D-ER acts by blocking potassium (Kv) channels exposed through MS-related demyelination, potentially improving conduction [8]. Kv channels are ubiquitously expressed within the CNS, thus any foci of demyelination which expose Kv channels may be influenced by D-ER. Previous published research on 4-Aminopyridine (4-AP), the active ingredient chemical constituent of D-ER, suggests improvement in more than just walking speed in pwMS [9–11]. The pharmacokinetics of D-ER compared to the immediate release formulation of 4-AP result in more constant systemic exposure [12,13]. Initial D-ER trials provided evidence of improvement in muscle strength [5,14,15] and these findings should be further explored. The goal of the present study

Abbreviations: pwMS, Persons with Multiple Sclerosis; MS, Multiple Sclerosis; CNS, Central Nervous System; D-ER, Dalfampridine-Extended Release; FDA, Food and Drug Administration; T25FW, Timed 25-Foot Walk; Kv, potassium; 4-AP, 4-Aminopyridine; 6 MW, Six Minute Walk; SSST, Six-Spot Step Test; MSWS-12, 12-item Multiple Sclerosis Walking Scale; 9HPT, Nine-Hole Peg Test; BBT, Box and Blocks Test; OS, Observational Sample; ES, Efficacy Sample; TWR, Timed Walk Responders; TWNR, Timed Walk Non-Responders; EDSS, Expanded Disability Status Scale.

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is to evaluate D-ER's effects on multi-dimensional aspects of gait and dexterity in a real world, clinical setting.

2. Methods

This study was conducted at the Joyce D. and Andrew J. Mandell Center for Comprehensive Multiple Sclerosis Care and Neuroscience Research (Mandell Center) located at the Mount Sinai Rehabilitation Hospital in Hartford, CT and was registered on www.clinicaltrials.gov, NCT01399957. The Saint Francis Hospital Institutional Review Board approved the project. All participants provided written informed consent.

2.1. Study design

This prospective, observational study of pwMS prescribed D-ER by their treating clinician, monitored participants for the outcomes listed in Table 1 at a pre-D-ER baseline, and at 3.5, 7, 10.5, and 14 weeks after starting D-ER. The outcome data presented in this manuscript were collected as part of a larger ongoing study examining the effects of D-ER on multiple domains over 18 months. Participants were enrolled between August 2010 and March 2013. Participants were monitored for the duration of the project regardless of their decision to continue using D-ER. Research visits lasted 1.5 to three hours. Participants were compensated for travel and time for research visits, however, no compensation was provided for medication or routine clinical care.

2.2. Participants

PwMS prescribed D-ER as a part of routine care were referred to the study by neurology providers at the Mandell Center. Key inclusion criteria were: (1) a clinical diagnosis of MS, (2) receive MS care at the Mandell Center, (3) receive a new D-ER prescription, (4) able to understand directions (score of 22 or greater on the Mini Mental State Examination), and (5) 18 years of age or older. Key exclusion criteria included: prior use of D-ER or 4-AP based medications. Fifty-two participants met study criteria and were enrolled (Fig. 1A). Thirteen participants were excluded from analysis: five did not start medication within 30 days of consenting, five withdrew, two were unable to complete the 14 week assessment and one subject's diagnosis was changed from MS. The final analytic sample included 39 participants followed for 14 weeks.

2.3. Outcome measures

The following gait outcomes (Table 1) were measured at each of the 5 time points. The T25FW assessed walking speed by averaging the time to complete two trials [16–18]. The Six Minute Walk (6 MW) assessed walking endurance by capturing the total distance traveled while walking laps in a 50 meter hallway over 6 minutes [18]. The Six-Spot Step Test (SSST) assessed dynamic gait through navigation of a 1 x 5 meter course requiring initiation of gait, changes in direction and weight shifting to kick cylindrical blocks off of targets marked on the floor [19]. A total of four trials were completed, two with each leg. The time to complete two consecutive trials was averaged for each leg and an overall task average was calculated [19]. The 12-item Multiple Sclerosis Walking Scale (MSWS-12) [20,21] assessed self-perceived difficulty walking over the past 2 weeks. Each situation was rated on a scale of 1 (no limitation) to 5 (extreme limitation). A score was calculated by subtracting the minimum possible score [12] from the patient's score, dividing that number by 48 and then multiplying by 100; thus scores ranged from 0 to 100 [20]. Walking tests were conducted only on ambulatory participants; they were instructed to walk as fast as safely possible utilizing the assistive device typically used, if any, during ambulation.

Fine and gross dexterity measures were also assessed at each of the five time points. The Nine-Hole Peg Test (9HPT) assessed dexterity and fine motor control by averaging the time to complete two non-consecutive trials of each hand [22,23]. The Box and Blocks Test (BBT) assessed gross manual dexterity [24,25] by capturing the total number of blocks (2.5 x 2.5 x 2.5 cm) moved from one compartment to an adjacent compartment using one hand in one minute. Prior to the first trial for each hand, participants were given 15 seconds of practice. Results were averaged for two trials on each hand separately [25]. The BBT was added part way through the study and therefore not performed on all participants.

Disease history, subject characteristics, and the subject's most recent Expanded Disability Status Score (EDSS) from a clinic visit (not research), if performed within the past 3 years, was extracted from the participant's medical record. Patients completed the Patient Determined Disease Steps (PDDS) for the study. Data presented in this manuscript evaluate change from baseline to 14 weeks. Supplemental data are provided that evaluate the period from baseline to 7 weeks.

Table 1
Outcome measures: domains of gait and dexterity domains, tests, and abbreviations.

Domain	Test	Abbreviation
Gait Speed	Timed 25-Ft Walk	T25FW
Endurance	Six-Minute Walk Test	6 MW
Dynamic Gait	Six-Spot Step Test	SSST
Self-Perceived Walking Ability	MS Walking Scale-12	MSWS-12
Fine Dexterity	Nine-Hole Peg Test	9HPT
Gross Dexterity	Box and Blocks Test	BBT

2.4. Statistical analyses

Thirty-nine participants completed both baseline and week 14 visits (observational sample; OS). Of the 39, an Efficacy Sample (ES) included the 31 subjects who remained on D-ER for the entire 14-week observational period. In order to investigate whether changes in gait and dexterity outcomes varied by traditional responder status, the 31 persons who remained on drug for 14 weeks were sub-divided based on walking speed. The timed-walk responder (TWR) group ($n = 20$) included participants who showed improvement in walking speed (T25FW) on three out of four visits while on D-ER compared to their single off-drug baseline T25FW performance; the timed walk non-responder (TWNR) group ($n = 8$) included participants who failed to meet criteria for gait speed improvement [5–7] (Fig. 1B). Two persons who were non-ambulatory (defined as unable to complete the T25FW) and 1 person who did not complete enough assessments to classify responder status were excluded from the responder sub-group analyses.

Baseline differences between TWR and TWNR sub-groups were analyzed using chi-squared tests for categorical variables (gender and disease subtype) and Mann-Whitney *U* test for continuous or ordinal variables (age, disease duration, EDSS, PDDS, and baseline gait and dexterity measures). Changes between baseline and the 14-week visit (and between baseline and the 7-week visit presented in supplemental tables) were analyzed using the Wilcoxon signed-rank test. All data analyses were performed using SPSS version 21 (SPSS, Chicago, IL). A two-tailed *p*-value less than or equal to 0.05 was considered statistically significant.

3. Results

3.1. Study enrollment and baseline demographics

Fig. 1A depicts study enrollment. Reasons for withdrawal are described in the methods. Briefly, 52 individuals were consented of whom 39 were included for analysis in the overall observational sample (OS); a subset of 31 (ES) remained on D-ER throughout the 14 week observation period. Of the 31 participants in the ES group, 20 were classified as a TWR, 8 classified as TWNR, and three (2 non-ambulatory and 1 who did not complete enough assessments) were excluded because they could not be classified.

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