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Fampridine and real-life walking in multiple sclerosis: Low predictive value of clinical test for habitual short-term changes

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ABSTRACT

Background: Fampridine improves walking speed in patients with multiple sclerosis (MS) in performance-based tests. The impact on habitual mobility and its correlation with clinical tests has not been analysed.
Objective: To investigate the association between clinical response criteria and habitual mobility in MS patients starting a fampridine treatment.
Methods: During a four-week baseline-to-treatment study, we assessed in 28 patients (median EDSS 4.75, range 4–6.5) walking tests as the Timed-25-Foot-Walk (T25FW) and mobility questionnaires at day 0, 14 (start of treatment) and 28. Habitual steps and distance per day, total activity and walking speed was measured by accelerometry over four weeks. Beside improvement in real-life mobility, we investigated if such measures differed between non-responders and responders defined by a 20% improvement in clinical tests.
Results: All clinical test, patient reported outcomes and total activity improved significantly ($p < 0.05$). 46% improved (any change >0) in three of four real-life measures. Change of the T25FW predicted only an increase of distance per day. Subjective rating of patients performed better by predicting distance and walking speed changes correctly.
Conclusion: Fampridine might improve walking in daily life of MS, but clinical tests are weak predictors. Accelerometry opens a new perspective on mobility measurment, but the current data do not show a consistent effect on non-performance based accelerometry outcomes.

1. Introduction

Walking impairment is a prevalent hallmark of multiple sclerosis (MS) that has life-altering consequences for social participation, employment status, and quality of life [1,2]. Independent from disease duration, persons with MS rate lower limb function as one of the most valuable bodily functions [3]. Fampridine has been approved as the first symptomatic treatment to improve walking in patients with MS. Improvement in walking was demonstrated in two placebo-controlled phase-3 trials, by a consistently faster walking speed in the Timed 25 Foot Walk (T25FW) among patients treated with fampridine in comparison to placebo [4,5]. Response to treatment based on 20% improvement of the T25FW occurred in about a third of patients. It seems to be sustained over up to 3 years and phase-4 data suggest an improvement of patient-perceived burden of disease [6]. A post-hoc analysis of the phase-3 data identified a 20% improvement of the T25FW as clinically relevant end closely related to changes in the patient reported Multiple Sclerosis Walking Scale (MSWS) [7]. Similar findings were recently reported for the 6-Minutes-Walking-Test (6MWT) [8]. However, there is an on-going debate which walking measures are most response sensitive and clinically relevant and if other performance-based tests than the T25FW with less floor effects might be better response measures [9]. While the US Food and Drug administration had agreed to the T25FW as primary endpoint and approved the treatment in 2010, the European Medicines Agency granted a year later a conditional authorization recommending "to investigate a broader primary endpoint that is clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment." [10] In how far fampridine leads to an improvement of real-life walking abilities and in how far clinical measures predict a better habitual walking, i.e. how ecologically valid these assessments are, has not been investigated yet [11–13]. There is an increasing interest in

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Table 1
Descriptive statistics of the cohort.

	($n = 28$)
Females n (%)	17 (61)
Age mean (sd) years	49 (8.6)
EDSS Baseline median (range)	4.75 (4–6.5)
Disease Duration since First Symptoms mean (sd) years	15.3 (9.9)
Disease Duration since Diagnosis mean (sd) years	11.0 (8.4)
Disease course	
Relapsing-remitting MS n (%)	3 (11)
Secondary Progressive MS n (%)	18 (64)
Primary Progressive MS n (%)	7 (25)
Walking Tests and PROMS:	
T25FW mean (sd) seconds	11.9 (7.5)
T25FW mean (sd) m/s	0.64 (1.02)
TTW mean (sd) seconds	20.7 (9.3)
TTW mean (sd) m/s	0.14 (0.32)
6MWT mean (sd) meters	250 (115)
6MWT mean (sd) m/s	0.69 (0.32)
MSWS mean (sd) score	52.8 (9.8)
HAQUAMS mean (sd) score	3.3 (0.8)
FAI mean (sd) score	25.4 (9.4)
Accelerometry	
Walkingsteps/day mean (sd) n	3316 (2237)
Distance/day mean (sd) meters	2542 (1583)
Velocity walking mean (sd) m/s	1.02 (0.15)
Activity temperature mean (sd)	5.3 (1.0)

EDSS = Expanded Disability Status Scale, T25FW = Timed 25 Foot Walk, TTW = 3 m Timed Tandem Walk, 6MWT = 6-Minute Walking Test, FAI = Frenchay Activity Index, HAQUAMS = mobility subscale from the Hamburg Quality of Life Questionnaire in Multiple Sclerosis, MSWS = Multiple Sclerosis Walking Scale.

approaches for objectively monitoring patients under real-world conditions [14] and mobile accelerometers have the potential for objective monitoring of free-living walking behaviour [15]. Recent studies provide comprehensive evidence that accelerometer output reflects walking behaviour, including self-report, clinical, and objective walking performance and gait parameters in persons with MS. [14] Considering treatment costs, placebo effects and adverse events, reliable and ecologically valid measures of mobility are needed. We aimed to investigate real-life mobility response in patients with MS starting fampridine treatment and to analyse the association between response criteria based on clinical performance tests and PROMS with real-life response.

2. Methods

2.1. Study design and patients

For this study we recruited 31 consecutive MS patients eligible for a fampridine treatment according to the Summary of Product Characteristics (SPC) at the out-patient clinic of the University Medical Center Hamburg Eppendorf, Department of Neurology. Inclusion criteria were an age between 18 and 65 years, a defined MS according to McDonald criteria [16] and walking impairment with an Expanded Disability Status Scale (EDSS) [17] between 4.0 (maximal walking distance 500 m) and 6.5 (at least 20 m with bilateral walking aid). The study was designed to assess short-term treatment response to fampridine treatment in a four week baseline to treatment design with assessments at Day 0, Day 14 and Day 28. During the baseline period (Day 0–14) patients received no treatment, which was started after assessments on Day 14. At all three visits, patient underwent a neurological examination including EDSS, a 6-Minute Walking Test (6MWT) [18], a 3 m Timed Tandem Walk (TTW) [19] and a Timed 25 Foot Walk (T25FT) [7]. A single board certified neurologist (MJ) performed all assessments. Additional patient reported outcomes (PROMS) were the mobility scale from the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS, four items, five step Likert scale, higher scores indicating higher disability) [20], the MS Walking Scale (MSWS, 12 items, five step Likert scale, higher scores indicating higher disability) [21] and the Frenchay Activity Index (FAI, 15 items, four step Likert scale, lower scores indicating higher disability, only at Day 14 and 28) [22]. For baseline to treatment analyses, PROMS from Visit 2 (representing baseline period) and Visit 3 (representing treatment period) were used. Finally, participants and neurologist gave a simple subjective ("yes" or "no") rating if the participant responded to treatment or not. To assess real-life walking performance, participants were provided with an actibelt® accelerometer that was worn during the whole 4-week period except at nights. The following real-life measures were extracted from the accelerometer and averaged over the baseline and treatment period: mean number of steps per day, mean total distance per day, activity temperature (sum score of total activity recorded by the three axes of the accelerometer) and mean daily walking speed (m/s) [23–26]. Fampridine treatment was started in the evening of the visit at Day 14. All participants gave written informed consent and the ethic commission of the Hamburg Chamber of Physicians positively evaluated the study.

2.2. Statistics

We performed descriptive statistics of the cohort with mean/sd, median/range or number/rates according to the nature of the data. Boxplots and one-sided pairwise Student's *t*-test were used to investigate baseline test-retests stability (Visit 1 vs. Visit 2) and change of clinical tests after initiation of treatment (mean of Visit 1 and 2 vs. Visit 3, respectively means of week 1 and 2 vs. means of week 3 and 4 for accelerometry data). The association between baseline tests and real-life measures was quantified by calculating coefficient of determination (R^2). Absolute and relative changes (baseline to treatment) were calculated for all measures. A 20% improvement of the T25FW and the 6MWT has been postulated as a minimal clinically important change and we used this relative cut-off to define responders for other tests and PROMS as well (Visit 2 vs. Visit 3) [7,8]. We tested if change of real-life measures differed significantly between non-responders and responders based on the 20% change criterion by one-sided *t*-tests. In addition, we computed R^2 to investigate in how far absolute and relative changes of clinical outcomes and PROMS were correlated with real-life parameters to overcome the restrictions of a strict cut-off. *p*-Values below 0.05 were considered statistically significant. All analyses were performed with Statistics in R (Version 3.2.1).

Table 2
Correlation of outcomes at baseline.

R^2 (*p*-value)	Activity temperature	Distance	velocity walking	Walking steps
T25fW	0.04 (0.296)	0.28 (0.005)*	0.48 (<0.001)*	0.31 (0.002)*
TTW	0.03 (0.423)	0.02 (0.494)	0.01 (0.728)	0.07 (0.216)
6MWT	0.01 (0.681)	0.38 (0.001)*	0.54 (<0.001)*	0.43 (<0.001)*
FAI	0.02 (0.494)	0.07 (0.194)	0.49 (<0.001)*	0.05 (0.275)
HAQUAMS	0.01 (0.646)	0.29 (0.004)*	0.56 (<0.001)*	0.22 (0.012)*
MSWS-12	0.01 (0.600)	0.26 (0.011)*	0.50 (<0.001)*	0.13 (0.071)

R^2-values from linear models, asterisks indicate *p*-values < 0.05.