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Original Research Paper

Fampridine response in MS patients with gait impairment in a real-world setting: Need for new response criteria?

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Abstract

Objective: The primary objective of this real-world study was to describe the response to fampridine and changes of gait parameters in multiple sclerosis (MS) patients' walking disability (Expanded Disability Status Scale (EDSS): 4–7) after treatment with fampridine for 2 weeks as recommended by the European Medicines Agency (EMA) and compare it with the overall physician's judgement.

Methods: A total of 211 adult MS patients were analyzed using a multimodal gait assessment including the timed 25-foot walk test (T25FW), 2-minute walking test (2-MWT), 12-item Multiple Sclerosis Walking Scale (MSWS-12), the GAITRite electronic walkway system, and the patients' clinical global impression (CGI). Multimodal gait assessment was compared with the clinician's impression of overall improvement after 2 weeks.

Results: In total, 189 subjects were included, of which 133 (70.37%) were responders to fampridine (RF), according to physician's judgement. Looking at independent multimodal gait assessment, RFs showed improvement of 12.60% in the T25FW, 19.25% in the 2-MWT, 21.12% in the MSWS-12, and 6.54% in their Functional Ambulation Profile (FAP) score. The combination of the T25FW and the MSWS-12 would offer the best sensitivity and specificity for determining response to fampridine according to both neurologists' and patients' classification.

Conclusion: This study provides new information on the use of fampridine in a real-world setting with a large patient sample on the potential benefit of using more definitive responder criteria to fampridine for the clinical setting.

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Introduction

Multiple sclerosis (MS) is a demyelinating inflammatory disease of the central nervous system (CNS), which causes walking impairment in up to 70% of subjects with this diagnosis[1] and may occur already early in the disease process.[2] Walking impairment treatment has been approached mainly by rehabilitation and exercise therapies, showing some degree of improvement.[3]

Symptomatic treatment with fampridine has demonstrated walking improvement in MS patients.[4–8] Fampridine (4-aminopyridine), a wide-spectrum potassium channel blocker,[9] prevents the release of potassium from potassium channels exposed due to the inflammatory demyelinating process in the CNS; consequently, disrupted action potential conduction may be partly restored, yielding improvements in ambulation.[10]

Currently, most data available on fampridine efficacy in MS patients are limited to information from placebo-controlled, randomized clinical trials in artificial clinical study environments,[5–7] which demonstrated

that roughly 35% to 42% of subjects are responders to fampridine (RF). However, in clinical practice, the clinician is responsible to take the decision of fampridine response according to EMA's recommendations, which states that fampridine must be discontinued in subjects not showing any improvement after 2 weeks of treatment.[11]

Studies in a real-world setting have been made, most of them applying Hobart's criteria of clinical significant improvement,[12–14] which consider an improvement ⩾20% in the timed 25-foot walk test (T25FW) as significant, thus yielding similar results to the trials performed by Goodman et al., and raising the question of a possible larger benefit in a real-world setting by applying more permissive RF criteria, modeled after EMA's recommendation, and possible improvement in other functions besides walking speed measured with the T25FW. Other trials documented different responder rates: In a small multicenter study, Fragoso et al.[15] reported a 70% RF rate using the T25FW, similar to another trial applying less strict criteria for defining RF, resulting in similar proportion of RF.[16]

No real-world study investigating patients in clinical practice has assessed response to fampridine using EMA's recommendations and physician's global judgement to characterize the response to fampridine treatment over time. This information is needed to offer a real-world-oriented solution for clinical decisions.

The primary objective of this study was to describe clinical response and changes in gait parameters in subjects with MS and walking disability using a multimodal walking assessment in a real-world setting, after being treated with fampridine, with response criteria based on EMA's recommendations.

Methods

We conducted an open-label, monocentric real-world study investigating the effect of fampridine treatment on patients with MS applying a comprehensive multimodal walking assessment at the MS Center Dresden, Germany. First results about the methodological aspects of the assessment were published previously.[17] The study was approved by the ethical committee of the University Clinic of Dresden, Germany. All participants provided written informed consent.

A total of 211 adult MS patients were recruited before starting treatment with fampridine between 2011 and 2014. Patients were eligible to participate in the study in case of a confirmed MS diagnosis, indication for fampridine treatment, and the ability to walk continuously for at least 2 minutes according to self-report. Patients were excluded if they had a contraindication for initiating treatment with fampridine, or had severe walking disability impairing performance of the walking tests. Patients were tested prior to the administration of a dose of 10 mg of Fampyra® (Biogen, Cambridge, MA, USA) twice daily (baseline), as well as 2 weeks following the initial test (time point 2).

As in everyday practice, treating neurologists classified the subjects as RF and non-responders to fampridine (NRF). Neurologists generated an overall assessment regarding walking performance after 2 weeks, leading to the decision whether to continue or stop fampridine treatment, based on EMA's European Public Assessment Reports (EPAR) on fampridine,[11] described above.

We divided our population according to their disability as recorded with the Expanded Disability Status Scale (EDSS),[18] as subjects with mild walking disability (EDSS ⩽ 4.5), moderate walking disability (EDSS = 5.0– 6.0), and severe walking disability (EDSS ⩾ 6.5); subjects were also divided according to their diagnosis as relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). Patients were further grouped according to either improvement or non-improvement according to their clinical global impression (CGI), a score based on the patient's impression of self-improvement,[19] after 2 weeks.

Multimodal walking assessment consisted of the following tests:

Walking speed. The T25FW is a component of the Multiple Sclerosis Functional Composite (MSFC) and has shown reliability of walking speed testing in people with MS.[20,21] Testing was performed according to the instructions provided by the MSFC,[20] for which the mean value in seconds of two attempts was used for analysis.

Qualitative analysis of gait: The computerized GAITRite (CIR Systems, Inc., Havertown, PA, USA) system is an instrumented walkway which enables quantitative assessment of spatiotemporal parameters of gait. The main outcome, the Functional Ambulation Profile (FAP), has been validated as key marker of gait impairment in MS patients.[22]

Walking endurance test. The 2-minute walking test (2-MWT) has shown good reliability and validity in testing walking endurance in patients

with MS.[23] To implement endurance testing in clinical practice, we decided to use the 2-minute instead of the 6-minute duration as the 2-MWT has demonstrated good correlation with longer endurance tests[24]

Self-walking evaluation by the patient. The impact of MS on the participants' perceived walking ability was assessed using the 12-item Multiple Sclerosis Walking Scale (MSWS-12) questionnaire[25] using a score from 0 to 100. As secondary outcome measures, we included the patients' CGI,[19] subjects with a CGI outcome from 5, slight improvement, or better, up to 7, were considered as having a positive CGI score.

For the collection and management of data, the Multiple Sclerosis Documentation System (MSDS3D) was used.[26] All statistical analyses were performed using the IBM SPSS Software for Windows (Version 23.0; IBM Corporation, Armonk, NY, USA). The significance level for all statistical tests was set at $p<0.05$. If not stated otherwise, arithmetic mean values and standard deviations (SD) were reported. Analyses of variance (ANOVAs) and *t*-tests for paired samples for normally distributed outcomes, as well as Kruskal–Wallis H tests and Wilcoxon's signed rank test for not normally distributed outcomes, were performed to test for multiple group differences and for score differences of the four walking tests between the first and the second time point, respectively. Comparisons between two groups were done using *t*-tests for independent samples and Mann–Whitney *U*-tests, respectively. Receiver operating characteristic (ROC) curves were computed to determine the sensitivity and specificity of each test in relation to neurologists' clinical judgement. The area under the curve (AUC) and Youden's *J* statistic were calculated to estimate the overall potential and the specific cut-off values for each test. We used Kendall's tau-b for correlational analyses between study outcomes and Fleiss' kappa for assessing the agreement between neurologists and patients on the dichotomized overall improvement of patients' walking abilities.

Results

A total of 211 subjects were screened, and 189 were included in the study. Twenty subjects were excluded due to non-compliance with appointments or medication or physical inability to perform the tests; one subject had a diagnosis other than definite clinical MS and another had a significant adverse effect after baseline examination (see below). Compliance with medication was 98.9% in included subjects during observation. Subjects in the mild disability group were younger than those in the other disability groups ($p=0.035$ and $p=0.003$, moderate and severe disability in the age subgroup, respectively,) and those with mild disability had a significantly shorter disease course than those with severe disability ($p=0.028$). Subjects with RRMS were also younger (47.07 ± 9.40 vs 57.11 ± 9.62), had a significantly lower EDSS (4.63 ± 1.28 vs 5.70 ± 1.06) than those with other diagnoses ($p<0.001$), and had a significantly shorter disease course than those with SPMS (11.22 ± 6.85 vs 15.38 ± 12.43; $p=0.011$). All other characteristics were comparable among groups (see Table 1).

Adverse effects are listed in Table 2, of which nausea was the most common ($N=5$, 2.65%). One subject had an epileptic seizure during observation; medication was suspended and subject failed to attend further appointments.

A total of 153 subjects (80.95%) showed improvement of 10% or greater in at least one test or more, out of the four possible, after 2 weeks, while 36 subjects (19.05%) failed to show minimal improvement of 10% in any test (see Figure 1).

The 2-MWT and the MSWS-12 had the largest proportion of subjects showing at least minimal improvement of 10% ($N=113$, 59.79% and $N=110$, 58.51%, 2-MWT and MSWS-12, respectively; see Figure 1).

There was a mean general positive and significant improvement in all subjects in all four walking tests ($p<0.001$; see Table 3). The greatest improvement was noted in their self-perceived walking abilities (MSWS-12: 15.21%, $p<0.001$). According to CGI scores, 117 subjects (61.9%) had subjective improvement: 79 subjects (41.8%) had a slight improvement, 34 (17.99%) were much improved, and 4 (2.12%) were very much improved after 2 weeks.

Our sample was divided according to their response to fampridine in 133 responders (70.37%) and 56 non-responders (29.63%), following physician's overall judgement of improvement.

RFs showed an average improvement of 12.60% (T25FW) in their speed, 19.25% in their mean distance (2-MWT), 21.12% in their self-perceived walking performance (MSWS-12), and 6.54% in their FAP score.

In contrast, NRFs did not show any significant improvement in any of the walking tests (see Table 3). RFs also scored a better mean CGI score than NRFs after the time frame of 2 weeks (median = 5, interquartile range (IQR) = 1 vs median = 4, IQR = 1, responders and non-responders, respectively; $p<0.001$).

Table 1. Sample characteristics.

		All patients	Mild disability	Moderate disability	Severe disability	Responders to fampridine	Non-responders to fampridine
		N = 189	*N* = 68	*N* = 70	*N* = 51	*N* = 133	*N* = 56
Age	Mean ± SD	53.55 ± 10.83	49.13 ± 1.37	54.08 ± 10.35	56–86 ± 10.19	53.89 ± 11.42	52.75 ± 9.32
	Range	25–75	25–71	29–74	25–71	25–74	33–75
Gender							
	Female	122 (64.55%)	40 (58.82%)	45 (64.29%)	37 (72.45%)	89 (66.92%)	33 (58.93%)
	Male	67 (35.45%)	28 (41.18%)	25 (35.71%)	14 (27.55%)	44 (33.08%)	23 (47.07%)
Diagnosis[a]							
	RRMS	77 (40.74%)	42 (61.76%)	27 (38.57%)	8 (15.69%)	58 (43.61%)	19 (33.93%)
	SPMS	61 (32.28%)	15 (22.06%)	21 (30%)	25 (49.02%)	39 (29.32%)	22 (39.29%)
	PPMS	50 (26.46%)	10 (14.71%)	22 (31.43%)	18 (35.29%)	35 (26.32%)	15 (26.79%)
Treatment							
	None	79 (41.8%)	16 (23.53%)	33 (47.14%)	30 (58.82%)	53 (39.85%)	26 (43.46%)
	Interferon	17 (8.99%)	8 (11.76%)	7 (10%)	2 (3.92%)	14 (6.77%)	3 (5.36%)
	Glatiramer acetate	28 (14.82%)	14 (20.59%)	10 (14.29%)	4 (7.84%)	19 (14.29%)	9 (16.07%)
	Natalizumab	17 (8.99%)	9 (13.24%)	5 (7.14%)	3 (5.88%)	15 (11.28%)	2 (3.57%)
	Fingolimod	21 (11.11%)	11 (16.18%)	7 (10%)	2 (3.92%)	12 (9.02%)	8 (14.29%)
	Mitoxantrone	5 (2.65%)	0	1 (1.43%)	4 (7.84%)	4 (3.01%)	1 (1.79%)
	Azathioprine	2 (1.06%)	1 (1.47%)	1 (1.43%)	0	1 (0.75%)	1 (1.79%)
	Study[b]	20 (10.58%)	9 (13.24%)	6 (8.57%)	6 (11.76%)	15 (11.28%)	5 (8.93%)
EDSS	Mean ± SD	5.22 ± 1.29	3.63 ± 0.63	5.73 ± 0.37	6.55 ± 0.15	5.15 ± 1.32	5.39 ± 1.19
	Range	2.0–7.5	2.0–4.5	5.0–6.0	6.5–7.0	2.0–7.0	2.5–7.5
Disease duration	Mean ± SD	12.92 ± 10.83	10.42 ± 5.88	13.86 ± 8.73	14.61 ± 7.26	13.14 ± 8.21	12.35 ± 7.1
	Range	1.0–39.0	1.0–27	1.0–39	3.0–35	1.0–39	1.0–28

MS: multiple sclerosis; SD: standard deviation; RRMS: relapsing-remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS; EDSS: Expanded Disability Status Scale.
[a]One subject with MS diagnosis, but MS course unclear.
[b]Subjects were taking part in a randomized, double-blind study. Medication received unknown.

Table 2. Adverse effects.

Adverse effect	*N* = 190
Nausea	5 (2.63%)
Vertigo	4 (2.11%)
Fatigue	2 (1.05%)
Headache	2 (1.05%)
Insomnia	2 (1.05%)
Epileptic seizure	1 (0.53%)
Anxiousness	1 (0.53%)
Diarrhea	1 (0.53%)
Tremor	1 (0.53%)
Paresthesia	1 (0.53%)
Total	20 (10.53%)

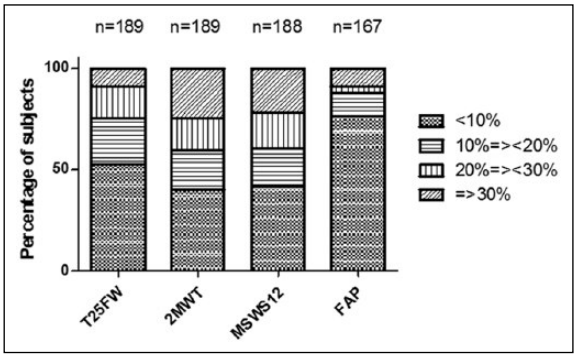

Figure 1. Proportion of subjects and percentage improvement shown in each walking test are represented in four different categories according to percentage of improvement from baseline to 2 weeks.
2-MWT: 2-minute walk test; FAP: Functional Ambulation Profile; MSWS-12: 12-item Multiple Sclerosis Walking Scale; T25FW: timed 25-foot walk test.

As mentioned above, 117 subjects (61.9%) had subjective improvement according to their CGI. Subjects with a positive CGI score performed significantly better at 2 weeks in comparison with their baseline measurement in all four walking tests ($p < 0.001$, see Table 4). This group of subjects showed a 16.16%

Table 3. Scores at baseline and 2 weeks later in walking tests.

	All subjects				Responders				Non-responders			
	N = 189				*N* = 133				*N* = 56			
	Baseline	2 weeks	Improvement[a]	*p*-value	Baseline	2 weeks	Improvement[a]	*p*-value	Baseline	2 weeks	Improvement[a]	*p*-value
T25FW[b]	12.61 ± 10.93	11.70 ± 11.67	7.22%	<0.001	12.62 ± 10.6	11.03 ± 10.52	12.60%	<0.001	12.57 ± 11.78	13.3 ± 14.04	–5.81%	0.548
2-MWT[c]	91.61 ± 46.95	105.13 ± 52.61	14.76%	<0.001	92.04 ± 46.85	109.76 ± 52.95	19.25%	<0.001	90.59 ± 47.58	94.15 ± 50.58	3.93%	0.250
MSWS-12[c]	72.46 ± 16.78	61.44 ± 19.33	15.21%	<0.001	72.11 ± 16.29	56.84 ± 17.91	21.12%	<0.001	73.32 ± 18.05	72.55 ± 18.2	1.05%	0.654
FAP[b]	74.34 ± 19.61	77.99 ± 19.21	4.91%	<0.001	74.60 ± 19.44	79.48 ± 18.23	6.54%	<0.001	73.66 ± 74.17	74.17 ± 19.85	0.69%	0.451
CGI[d]	NA	4.68 ± 1.13			NA	5.19 ± 0.74			NA	3.51 ± 1.02		<0.001

T25FW: timed 25-foot walk test; 2-MWT: 2-minute walking test; MSWS-12: 12-item Multiple Sclerosis Walking Scale; FAP: Functional Ambulation Profile; CGI: clinical global impression.
[a]Consists of mean score difference from baseline to 2 weeks, expressed as percentage.
[b]Wilcoxon's test for paired differences.
[c]*t*-test for paired differences.
[d]Mann–Whitney *U*-test for the comparison between responders and non-responders.

mean improvement in their T25FW, 20.67% in the 2-MWT, 21.74% in the MSWS-12, and 5.49% in the FAP score. However, estimates of the CGI improvement group were not significantly better than those of RF in any of the four walking tests during the 2-week period resulting from the high overlap between those two subgroups; 113 patients who showed a positive CGI score (96.58%) were also in the RF group.

Cut-off values for the classification into RFs and NRFs by neurologists' global judgement were determined with ROC curves (Youden's *J*). The T25FW (AUC = 0.804, $p < 0.001$) and the MSWS-12 (AUC = 0.801, $p < 0.001$) yielded the best overall sensitivity and specificity of a single test (see Table 5). In case of multiple tests, a combination (sum of percental improvement) of T25FW and MSWS-12 (AUC = 0.858, $p < 0.001$, $J = 18.20\%$) was in favor for indicating response to fampridine providing even better classification than a set of all four tests (AUC = 0.815, $p < 0.001$) or any other combination. For the analysis of patients' self-perception, we used the dichotomized CGI (did improve/did not improve) with the ROC curves and found similar results: a combination (sum of percental improvement) of T25FW and MSWS-12 was the most powerful test setting. In addition, there was a substantial agreement (Fleiss' kappa = 0.61) between neurologists and patients about the individual improvement of patients' walking abilities.

There was a significant correlation in three of four tests and the CGI, but not between the EDSS and the walking performance tests (see Table 6). Correspondingly, patients' disability did not influence performance measured as relative improvement in any of the four walking tests or in the CGI. Furthermore, the type of diagnosis (RRMS, SPMS, or PPMS) did not have a significant effect on the response of subjects as measured in any of the four walking tests or the CGI.

Discussion

The main objective of this study was to describe fampridine response in MS patients in clinical practice assessed by physicians' global judgement, and according to EMA's recommendations on fampridine.

This real-world study adds new important information to the current literature about the effects of fampridine on walking function in clinical practice and contributes to build on the existing real-world experience with the use of this drug, describing the largest MS sample in that aspect to our knowledge. Our study provides evidence that physicians' global judgement

Table 4. Patients with and without improvement of their CGI score.

	CGI improvement[a]				CGI non-improvement			
	N = 117				*N* = 72			
	Baseline	2 weeks	Improvement[b]	*p*-value	Baseline	2 weeks	Improvement[b]	*p*-value
T25FW[c]	12.50 ± 10.93	10.48 ± 7.84	16.16%	<0.001	12.78 ± 11.01	12.92 ± 12.72	–1.10%	0.162
2-MWT[d]	92.18 ± 47.20	111.23 ± 54.29	20.67%	<0.001	90.69 ± 46.84	95.22 ± 48.52	5.00%	0.084
MSWS-12[d]	71.22 ± 16.90	55.74 ± 17.46	21.74%	<0.001	74.73 ± 16.48	70.62 ± 18.75	5.50%	0.017
FAP[c]	74.07 ± 18.95	80.40 ± 19.00	8.55%	<0.001	71.29 ± 20.36	73.87 ± 19.15	3.62%	0.035

CGI: clinical global impression; T25FW: timed 25-foot walk test; 2-MWT: 2-minute walking test; MSWS-12: 12-item Multiple Sclerosis Walking Scale; FAP: Functional Ambulation Profile.
[a]CGI Improvement or positive score was defined as a slight improvement or greater in the CGI score given by the patient at 2 weeks.
[b]Consists of mean score difference from baseline to 2 weeks, expressed as percentage.
[c]Wilcoxon's test for paired differences.
[d]*t*-test for paired differences.

Table 5. AUC and cut-off scores for gait metrics according to physicians' judgement and patients' CGI score.

	Physicians' judgement					CGI				
	AUC		Cut-off			AUC		Cut-off		
	Area	95% CI	Score	Percental improvement[a]	*p*-value	Area	95% CI	Score	Percental improvement[a]	*p*-value
T25FW[b]	0.804	0.738–0.871	1.35	10.69%	<0.001	0.716	0.639–0.793	0.71	5.65%	<0.001
2-MWT[c]	0.706	0.622–0.790	8.299	9.06%	<0.001	0.682	0.601–0.764	6.43	7.02%	<0.001
MSWS-12[d]	0.801	0.733–0.869	11.42	15.77%	<0.001	0.743	0.671–0.816	12.4	16.68%	<0.001
FAP[e]	0.628	0.539–0.717	6.698	9.01%	0.01	0.564	0.474–0.654	1.67	2.24%	0.167
T25FW+ MSWS-12	0.858	0.803–0.914	NA	18.20%	<0.001	0.76	0.690–0.831	NA	9.97%	<0.001

CGI: clinical global impression; AUC: area under the curve; T25FW: timed 25-foot walk test; 2-MWT: 2-minute walking test; MSWS-12: 12-item Multiple Sclerosis Walking Scale; FAP: Functional Ambulation Profile.
[a]Calculated per Youden's *J*.
[b]Score in seconds.
[c]Score in meters.
[d]Percentual score, according to the MSWS-12.
[e]Score from 0 to 100.

Table 6. Correlations between patients's disability measured by EDSS and walking test score differences at two weeks.

	Correlations				
	EDSS	CGI	T25FW	2-MWT	MSWS-12
CGI	–0.026	1			
T25FW[a]	0.052	0.311[b]	1		
2-MWT[a]	0.007	0.230[b]	0.371[b]	1	
MSWS-12[a]	0.074	0.337[b]	0.230[b]	0.170[b]	1
FAP[a]	0.093	0.110	0.263[b]	0.165[b]	0.031

EDSS: Expanded Disability Status Scale; CGI: clinical global impression; T25FW: timed 25-foot walk test; 2-MWT: 2-minute walking test; MSWS-12: 12-item Multiple Sclerosis Walking Scale; FAP: Functional Ambulation Profile.
[a]A difference between baseline score and the score after 2 weeks is represented.
[b]Correlation is significant at the 0.01 level (two-tailed).

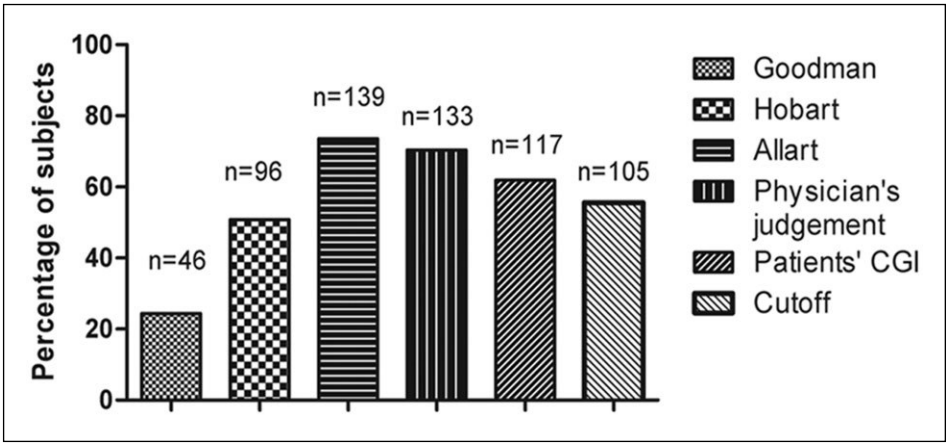

Figure 2. Percentage of responders in our sample applying different responder criteria: Goodman: subjects showing an improvement of 20% or more in the T25FW; Hobart: subjects showing an improvement of 6.9 points or greater in the MSWS-12; Allart: subjects showing an improvement of 15% or greater in the T25FW, the 2-MWT, or the MSWS-12; Physicians' judgement: subjects showing a clinical significant improvement in the T25FW, 2-MWT, MSWS-12, and FAP, according to physician's judgement after 2 weeks of treatment. This criterion was applied in this study; Patients' CGI: represents subjects who received a CGI score of 5 or greater; Cut-off: subjects showing an improvement greater than 21% (percentage improvement in T25FW + percentage improvement in MSWS-12), according to our ROC curve analysis.
2-MWT: 2-minute walk test; FAP: Functional Ambulation Profile; MSWS-12: 12-item Multiple Sclerosis Walking Scale; T25FW: timed 25-foot walk test.

is a reliable outcome for determining response to fampridine over time, as RF performed significantly better in all multimodal gait parameters compared to those in our NRF subgroup.

Our sample consisted mostly of females with a diagnosis of RRMS, similar to current epidemiological reports.[27] Most subjects did not receive a DMT, due to the majority of them having a progressive form of the disease.[28] Age and EDSS differences in different disability and diagnosis groups, although significant, did not cause a significant effect in the response to fampridine.

Most subjects (80.95%) showed improvement in at least one of the tests included in the multimodal walking model and most of those individuals had improvement in three of the four walking tests, being the 2-MWT and the MSWS-12, the tests with the larger proportion of subjects showing at least 10% improvement, and most had an improvement of ⩾30% in their scores at 2 weeks in the mentioned tests. In overall score improvement of all patients, all tests showed a significant improvement after 2 weeks, although the 2-MWT and the MSWS-12 showed as well the largest percentage improvement (14.76% and 15.21% improvement in 2-MWT and MSWS-12, respectively). This finding suggests that fampridine exerts its benefits in a variety of gait parameters besides speed; moreover, the T25FW, the MSWS-12, the 2-MWT, and the CGI correlated significantly with each other.

Following physicians' overall judgement, 70.37% of subjects were characterized as RFs. Our clinical responder subgroup showed significant improvement in all four walking tests. The MSWS-12 questionnaire and the 2-MWT showed the greatest improvement, while walking speed alone had an overall improvement below 20%, which has been described as a clinically meaningful change.[29] Our findings suggest that following criteria based on physicians' global judgement manifest clinical relevant response of fampridine regarding other gait characteristics, as our subjects showed the greatest response in walking endurance and self-perceived disability. A similar proportion of RF was found by Allart et al.,[16] who defined RFs as those with an improvement of 15% in the T25FW, 2-MWT, or the MSWS-12.

Subjective improvement defined by patients with the CGI, and significant response in the MSWS-12 criteria proposed by Hobart,[30] was lower than responder rate as defined by the neurologist (61.9% vs 50.79% vs 70.37%, respectively, see Figure 2), which suggests that clinical judgement was not influenced by patient's assessment of improvement only, and that it also includes information about walking endurance and gait speed.

The combination of the T25FW and the MSWS-12 offered the best sensitivity and specificity for determining response to fampridine according to both neurologists' and patients' classification. Although

patients receiving a positive CGI score had a similar performance to RF, and a great proportion of CGI responders were also RF (96.58%), AUC values were greater for RF according to physicians' judgement as compared to response defined by the CGI. There was no significant difference in performance between RF and CGI responders due to the high overlap between those two rating-based subgroups. Similar to our findings, Baert et al.[3] reported that the MSWS-12 and long capacity tests are the most sensitive for evaluating gait improvement in MS patients receiving physical rehabilitation.

Neither level of disability nor diagnosis had an effect on the response to fampridine in any of the tests included in the multimodal walking model, or the CGI. A similar observation was made by Goodman et al.[5–8] in previous trials, which suggests that all subsets of MS patients with walking disability might profit from the use of fampridine.

As mentioned above, it has been suggested that the threshold for determining a clinical significant response to fampridine is a 20% speed improvement in the T25FW[6,7] and a 6.9-point improvement in the MSWS-12.[30,31] Applying different criteria to determine RFs in our sample would affect the proportion of RFs and NRFs, with the greatest proportion of RF being determined by physicians' judgement (see Figure 2).

There is a gap between subjects showing any improvement, as defined by the EMA,[11] and those with improvement ⩾20% in the T25FW. Allart et al., applying different response criteria, as described above, reported a similar response rate to our study. This suggests that in a real-world clinical setting, a larger number of subjects demonstrate positive effects from fampridine than previously suggested in controlled clinical trials.

In our study, a control group was not included. Conceptually, without such a group, beneficial alterations in walking behavior, as observed in this study, cannot be attributed to onset of fampridine treatment directly. Given the extensive body of literature in strong support of such an effect of fampridine,[5–8,12,13,16,32–34] and the methodological emphasis of the current work, this limitation might not be critical.

To reduce complexity in the analysis of spatiotemporal gait patterns, we limited our analysis to the FAP score as a validated outcome for assessing gait in MS patients;[22,35] an assessment of each gait parameter itself would be out of the scope of this paper.

This study provides new information on the usefulness of multimodal walking testing with fampridine treatment and suggests that current treatment response criteria for fampridine should be reevaluated for the clinical setting in subjects with MS and gait impairment in order to match clinical study outcomes and the regulations of health authorities like the EMA.[36] We found evidence that physicians' global judgement is a reliable outcome for determining response to fampridine over time, and a combination of objective tests and patient-reported outcomes might become the most useful and efficient standardized test setting for such "real-world" problems.

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Declaration of Conflicting Interests

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