Ther Adv Chronic Dis
2019, Vol. 10: 1–11
DOI: 10.1177/2040622319835136

Nonwalking response to fampridine in patients with multiple sclerosis in a real-world setting

Francisco Alejandro Rodriguez-Leal, Rocco Haase, Katja Akgün, Judith Eisele, Undine Proschmann, Thorsten Schultheiss, Raimar Kern and Tjalf Ziemssen

Abstract

Objectives: Mobility impairments constitute a long-term burden in patients with multiple sclerosis (MS). Currently there is evidence that the drug fampridine may improve nonwalking symptoms in MS patients. The main objective of this study is to analyze whether participants showing a beneficial walking response to fampridine, also show a positive response in nonwalking assessments in a real-world clinical setting.

Methods: Subjects enrolled were part of a study analyzing gait parameters, for which response to treatment with fampridine was monitored after a period of 2 weeks. Neurologists then decided whether patients were responders to fampridine (RF) according to their global impression of patients' gait improvement. As nonwalking outcomes, we included the nine-hole peg test (9-HPT), the EuroQoL five dimensions questionnaire (EQ-5D) for quality of life, The Würzburger Fatigue Inventory for MS (WEIMuS), the Center for Epidemiologic Studies depression scale (CES-D), and the Paced Auditory Serial Addition Test (PASAT). Minimal clinically important difference (MCID) was evaluated for each test.

Results: A total of 189 participants were included: 122 were women (64.55%), with a mean age of 53.55 (±10.83). RFs showed significant improvement in all of the nonwalking outcomes ($p < 0.05$), except for a nonsignificant improvement in nondominant upper limb function and PASAT; the largest score improvement was seen in the physical and cognitive sections of the WEIMuS (25.69% and 29.81%, respectively, $p < 0.001$).

Conclusion: We provide evidence that physician's global judgement of walking improvement is a reliable measure for determining response to fampridine in nonwalking parameters, with fatigue showing the greatest score improvement after 2 weeks.

Keywords: 4-aminopyridine, cognition, depressive symptoms, fampridine, fatigue, multiple sclerosis, quality of life, upper extremity

Received: 30 October 2018; revised manuscript accepted: 6 February 2019.

Correspondence to:
Tjalf Ziemssen
Center of Clinical Neuroscience, Department of Neurology, University Hospital Carl Gustav Carus, Fetscherstr. 74, Dresden, 01307, Germany
Tjalf.Ziemssen@uniklinikum-dresden.de;

Francisco Alejandro Rodriguez-Leal
Rocco Haase
Katja Akgün
Judith Eisele
Undine Proschmann
Thorsten Schultheiss
Raimar Kern
Center of Clinical Neuroscience, University Hospital, Carl Gustav Carus, TU Dresden, Germany

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system leading to a large array of symptoms in young adults. Up to 75% of patients with this disease suffer from gait impairment in the long term.[1] Nevertheless, nonwalking symptoms constitute a long-term burden on patients affected with this disease.[2] Fatigue, cognitive impairment, upper limb dysfunction and depression have been demonstrated to be prevalent in a high proportion of participants[3] and to be critically important for the quality of life (QoL) of MS patients as well.[4,5] Some nonwalking symptoms appear to interact with each other.[6] Although they seem to occupy a second level of importance in the management of MS symptomatology, they might be more incapacitating than walking impairment itself from a patient's perspective.[7] Treatment of nonwalking symptoms is currently

approached by multidisciplinary teams while symptoms must be approached individually.

In recent years, more and more evidence has emerged in favor of the benefits of the drug fampridine, a potassium channel blocker, on walking impairment in MS patients.[8–11] In addition, studies have successfully replicated such positive results and offered some data suggesting a possible benefit of this drug on other functional outcomes in addition to walking speed.[12–16]

Information derived from double-blinded, controlled clinical trials has not been very strong regarding fampridine benefits on nonwalking outcomes so far[11,16,17]; however, open-label studies investigating nonwalking outcomes as secondary objective have already shown improvement in upper limb function, fatigue, QoL, and cognitive function.[12,13,15] One open-label study by Jensen *et al*. studied nonwalking outcomes as a primary objective, showing improvement in cognitive function, upper limb dexterity and other motor outcomes. However, this study lacks information on QoL and fatigue.[18] Two recent double-blinded studies investigating the effects of fampridine on cognitive function delivered inconclusive or negative results, but provided information on possible future applications of the drug such as improvement in muscle strength.[16,19] Whereas these studies offer valuable information on the effects of fampridine on multiple functions, no standardized test protocol to evaluate nonwalking parameters exists for assessing response to fampridine in nonwalking outcomes currently and different study protocols make assessment of the current evidence challenging.

Currently, neurologists working with MS patients in clinical practice might find it challenging to apply such available data for fampridine to their real-world, clinical setting.[20] Clinical data offering information about the effects of fampridine on nonwalking symptoms, derived from the daily clinical practice, are lacking. Moreover, there is little information on which degree of improvement can be considered as a positive response to fampridine on nonwalking outcomes.

The main objective of this study is to evaluate whether participants showing a beneficial response to fampridine in walking performance also show a positive response in nonwalking assessments, in a group of patients with MS and gait impairment in a real-world setting. In theory, we assume that the greatest benefits from fampridine in our nonwalking assessment will be described by the EuroQoL five dimensions questionnaire (EQ-5D)[21] owing to the included question regarding mobility and the nine-hole peg test (9HPT) assessing the upper limb (motor) function followed up by fatigue outcomes.

As a secondary objective, we evaluate whether the physician's judgement of walking improvement is a reliable outcome for improvement in nonwalking assessments.

Methods

We conducted an open-label, monocentric, real-world study investigating the effects of fampridine on nonwalking parameters in a sample of MS patients with gait impairment who were eligible for fampridine treatment. A total of 211 consecutive MS patients were initially enrolled from the outpatient clinic in the Multiple Sclerosis Center in Dresden, Germany. The sample used for this study took part in a related study analyzing gait parameters in patients with MS.[22] The data contained in this study consists of a previously specified subanalysis of the cohort presented by Rodriguez-Leal *et al*.,[22] and as such, both studies share the same inclusion criteria. In short, criteria for including participants were having a definite diagnosis of MS, walking impairment [Expanded Disability Status Scale (EDSS) 4.0–7.5], not having contraindications for starting treatment with fampridine, and ability to perform walking tests. Exclusion criteria were not having a definite MS diagnosis and having contraindications for treatment with fampridine. This study, as well as the related study analyzing gait parameters, was approved by the ethical committee of the University Clinic of Dresden, Germany. This study shares the same ethics committee approval number as Rodriguez-Leal *et al*.[22] All participants included in both studies were provided with information about the corresponding study by their treating neurologist and signed an informed consent.

As mentioned above, participants enrolled in this study underwent a multimodal gait assessment and response to treatment with fampridine was monitored after a period of 2 weeks treatment.[22] After being enrolled, patients underwent a walking and nonwalking assessment (baseline) and then were instructed to take 10 mg of Fampyra®

(Biogen, Cambridge, MA, USA) every 12 h for 14 days. After this time period, participants were evaluated again (time point 2), following the same procedures as in baseline, as described further in the following. One out of five treating neurologists then decided whether patients were responders to fampridine (RFs) or nonresponders to fampridine (NRFs), according to the physicians' global impression of patients' gait improvement after the mentioned treatment period, as is done in daily clinical practice. This response criteria was modeled according to the European Public Assessment Report (EPAR) of the European Medicines Agency (EMA) on fampridine, which states that treatment with fampridine should be suspended in participants not showing walking improvement after a period of 2 weeks.[23] The physicians' global impression of patients' gait improvement was determined by each neurologist's judgment based on patient's performance in four walking tests after treatment with fampridine, based on the Clinical Global Impression Scale.[24] Further methodological aspects of the study by Rodriguez-Leal *et al.* can be reviewed elsewhere.[22]

As nonwalking outcome measures for this study, the following tests were included.

- 9HPT: a quantitative measure of arm and hand function, which requires the patient to insert a number of pegs into holes and remove them afterwards. Average of two trials in seconds from both dominant (9HPT_D) and nondominant hands (9HPT_ND), as described in the Multiple Sclerosis Functional Composite (MSFC),[25] were used for this study.
- The EQ-5D,[21] a standardized measure of health-related quality of life (HRQoL), is based on a system that defines health in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For means of this study, we used the EQ-5D index as the score, described by Greiner *et al.* for the German population.[26]
- The Würzburger Fatigue Inventory for MS (WEIMuS)[27] is a validated questionnaire for German-speaking patients that measures fatigue in two dimensions: cognitive and physical fatigue. We included both the physical and cognitive sections of this test.
- The Center for Epidemiologic Studies depression scale (CES-D) is a questionnaire designed to measure depressive symptoms in the general population.[28] It has been validated and higher scores result in more depressive symptoms. For this study we used the version validated in German language.[29]
- The Paced Auditory Serial Addition Test (PASAT) was included as a cognitive function outcome measure. It assesses auditory information processing speed, as well as calculating ability. It is expressed as a score ranging from 0 to 60, with higher scores representing better performance. In this study, the PASAT version applying intervals of 3 s was employed as described in the MSFC.[25]

We established subgroups of patients according to their disability, as measured with the EDSS, as participants with mild disability (EDSS $\leqslant$ 4.5), moderate disability (EDSS 5.0–6.0) and severe disability (EDSS $\geqslant$ 6.5) and according to their diagnosis as relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). Subgroups are presented according to the analysis in Rodriguez-Leal *et al.*[22]

For this study, a minimal clinically important difference (MCID) for the EQ-5D was defined as an improvement of 0.08 after 2 weeks, as it was suggested by Kim *et al.*[30] As there is no defined MCID for the CES-D or WEIMuS, we considered the MCID for these tests at a 10% improvement or greater after 2 weeks, under the principle that participants with higher base scores might not be able to show a greater response than 10% in those tests, with score data being represented as a ratio. For the 9HPT and PASAT, we considered a MCID of 12.5% and 11.4%, respectively, which means a greater change than participants taking placebo in a double-blinded trial performed by Goodman *et al.*[8] Even though other open-label studies exploring the MCID for the 9HPT have been performed,[31] we decided to include a MCID based on the data by Goodman *et al.* owing to its double-blinded design.

Statistical analysis

A repeated-measures analysis of variance (ANOVA) was performed in order to search for the effect of disability and diagnosis between the two time points (baseline and 2 weeks). A factorial ANOVA was performed to test for the effect each subgroup

of patients had on walking improvement after 2 weeks. A Mann–Whitney U test was performed to search for differences in nonnormally distributed samples and Student's t test for normally distributed samples. A tau b correlation was used to search for correlations between nonwalking outcomes with each other and disability by EDSS. If not stated otherwise, reported values represent means and standard deviations.

Results

Population

A total of 211 participants were screened, and 189 were included in the study. Twenty participants were excluded owing to noncompliance with appointments or medication or physical inability to perform the tests; one participant 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 participants during observation. Subjects in the mild disability group were younger than those in the other disability groups ($p = 0.035$, $p = 0.003$, moderate and severe disability in the age subgroup, respectively, and $p < 0.001$ for both moderate and severe disability in the EDSS) 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 *versus* 57.11 ± 9.62) and had a significantly lower EDSS (4.63 ± 1.28 *versus* 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 *versus* 15.38 ± 12.43; $p = 0.011$). A total of 97 participants (51.32%) had a documented motor deficit in at least one of their upper extremities, of which 41 participants (42.27%) were in the severe disability group, 40 (41.24%) were in the moderate disability group, and 16 (16.49%) were in the mild disability group. All other characteristics were comparable among groups. See Table 1 for demographics. Adverse effects are listed in Table 2, of which nausea was the most common ($N = 5$, 2.65%), followed by vertigo. One participant had an epileptic seizure during observation; medication was suspended and the participant failed to attend further appointments.

Change in nonwalking parameters

After 2 weeks, participants in the whole sample showed a significant improvement in hand dexterity of 6.42% (34.28 s (15.33) *versus* 32.08 s (12.55) from baseline to 2 weeks, respectively, $p < 0.001$) in the dominant hand, and a nonsignificant positive change of 4.59% in the nondominant hand ($p = 0.092$), as well as significant improvements in the CES-D ($p = 0.010$) of 10.41%, the EQ-5D (8.45%, $p < 0.001$), the PASAT (3.26%, $p = 0.004$), and in the cognitive and physical sections of the WEIMuS ($p < 0.001$, improvement of 19.45% and 17.01%, respectively), the latter showing the greatest percental improvement of all nonwalking outcomes. See Table 3.

Seventy (37.04%) participants had a MCID improvement after 2 weeks in the EQ-5D, according to the criteria listed above, 40 (21.16%) and 23 (12.17%) in the dominant and nondominant hands in the 9HPT, respectively, 43 (22.75%) in the PASAT, 93 (49.21%) in the CES-D, 96 (50.79%) and 100 (52.91%) in the cognitive and physical sections of the WEIMuS, respectively.

Participants with moderate disability had a significant greater mean score improvement at 2 weeks with their nondominant hand in the 9HPT ($p = 0.015$) than those with severe disability. In contrast to this finding, disability did not have an effect in the dominant hand in the 9HPT, the EQ-5D, PASAT, the CES-D, or the WEIMuS. Patients with diagnosis of SPMS had a significant greater score improvement after 2 weeks in the PASAT in comparison with PPMS patients ($p = 0.004$). Diagnosis did not have an effect on the response to fampridine in the remaining nonwalking tests.

There was a significant correlation between score change in the CES-D, and the physical section of the WEIMuS ($p = 0.049$) and between both sections of the WEIMuS ($p < 0.001$). There was no significant correlation between disability by EDSS and any of the nonwalking outcomes. See Table 4.

Walk responders and nonresponders to fampridine

RFs were defined according to their walking improvement after treatment with fampridine, as described previously.[22] In the nonwalking outcomes, RFs showed the greatest improvement in the physical and cognitive sections of the WEIMuS (25.69% and 29.81%, respectively, $p < 0.001$).

Table 1. Demographics.

		All patients	Mild disability	Moderate disability	Severe disability	Responders to fampridine	Nonresponders 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 [b]							
	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[a]	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

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

Table 2. Common side effects.

Side 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%)

RFs also showed a significant improvement of 5.25% in the dominant hand ($p = 0.025$) in the 9HPT, and a significant 11.53% improvement in QoL, a 17.68% improvement in the CES-D ($p < 0.001$), a nonsignificant improvement in the nondominant hand in the 9HPT ($p = 0.344$) and a nonsignificant improvement in the PASAT ($p = 0.632$) (Table 3).

In contrast, NRF did not show any significant improvement in any of the nonwalking tests, except for a 9.26% improvement in the PASAT ($p = 0.002$) see Table 3.

According to the criteria listed above, in the whole sample, 62 participants (46.62%) showed at least MCID in the EQ5D, as well as 33 (24.81%) and 19 (14.29%) in the dominant and nondominant hands in the 9HPT, respectively, 27 patients (20.30%) in the PASAT, 74 participants (55.64%) in the CES-D as well as 80 (60.15%) and 83 patients (62.41%) in the cognitive and physical sections of the WEIMuS, respectively.

As a result, participants with performances above the MCID in each test had a significant greater improvement at 2 weeks than the participants below MCID improvement in all tests ($p < 0.001$; see Table 5).

In the 9HPT dominant hand, 33 participants (82.50%) showing MCID were also RFs, 19 (82.61%) were RFs with their nondominant hand, 27 in the PASAT (62.79%), 74 participants in the CES-D (79.57%), 62 in the EQ-5D (88.57%), 80 (80.81%) and 83 (83.00%) participants in the cognitive and physical sections of the WEIMuS, respectively.

Discussion

The main objective of this study was to describe our experience treating MS patients with gait impairment in a real-world setting and to investigate whether walking-responders to fampridine benefit on nonwalking outcomes after a test treatment period of 2 weeks. Our findings suggest that RFs also benefit on nonwalking outcomes, most notably on fatigue and QoL, showing a broader spectrum of action for fampridine as described previously.

Looking at the whole population, the most notable positive change was seen in fatigue, in both the cognitive and physical sections of the WEIMuS questionnaire (19.45% and 17.01% improvement at 2 weeks, respectively), followed by positive and significant changes in depressive symptoms and QoL (10.41%, and 8.45% improvement in the CES-D and the EQ-5D at 2 weeks, respectively). Hand dexterity was modestly improved in the dominant hand, as well as cognitive outcomes. This supports the observation that the effects of fampridine may have a broader spectrum of effect on participants with MS than walking speed alone in this sample of patients analyzed directly in clinical practice. The effects of fampridine on fatigue in MS were the subject of an earlier trial attempting to demonstrate the effects and safety of the drug on this patient population, showing efficacy in participants with high serum levels of the drug[17]; open-label studies with fampridine analyzing fatigue as a secondary objective have yielded similar results,[13,32] although they lacked a control group and smaller patient samples were studied. The listed studies, however, used different fatigue tests to those used in this study. A positive effect of fampridine on hand dexterity has been suggested previously in open-label studies.[12,13]

Similar findings have been reported in QoL and depression,[12,13] whereas results on cognitive scores have been conflicting.[13,18] Despite the progress shown by those studies, standardized measures have not been defined for testing of depression, fatigue, and cognition in MS patients receiving fampridine.

Table 3. Walk responders and nonresponders to fampridine.

	All participants		p	Walking responders[a]		p	Walking nonresponders[a]		p
	N = 189			N = 133			N = 56		
	Baseline	2 weeks	pb	Baseline	2 weeks	pb	Baseline	2 weeks	pb
9HPT_D	34.28 ± 15.33	32.08 ± 12.55	<0.001	33.14 ± 13.25	31.40 ± 12.30	0.025	37.08 ± 19.40	33.76 ± 13.14	0.125
9HPT_ND	36.58 ± 21.58	34.93 ± 15.83	0.092	36.36 ± 23.47	33.91 ± 14.72	0.344	37.14 ± 16.22	37.54 ± 18.27	0.983
EQ-5D	0.70 ± 0.23	0.77 ± 0.19	<0.001	0.72 ± 0.21	0.80 ± 0.17	<0.001	0.66 ± 0.25	0.68 ± 0.23	0.336
WEIMuS Cognitive	12.63 ± 8.06	9.61 ± 8.41	<0.001	11.45 ± 7.42	7.61 ± 7.06	<0.001	15.33 ± 8.85	14.88 ± 9.41	0.942
WEIMuS Physical	17.18 ± 7.53	13.99 ± 8.04	<0.001	16.24 ± 7.38	11.92 ± 7.46	<0.001	19.44 ± 7.46	19.43 ± 6.93	0.790
CES-D	15.84 ± 8.74	13.8 ± 8.29	.010	14.59 ± 8.39	12.01 ± 7.34	<.001	17.62 ± 9.25	18.44 ± 8.85	.778
PASAT	45.15 ± 12.17	46.62 ± 11.91	0.004	46.40 ± 11.39	46.81 ± 11.98	0.632	42.22 ± 13.48	46.13 ± 11.84	0.002

[a]According to the physician's global judgment of walk improvement.
[b]Wilcoxon's test for paired differences.
CES-D, Center for Epidemiologic Studies depression scale; EQ-5D, EuroQoL five dimensions questionnaire; 9HPT_D, nine-hole peg test dominant hand; 9HPT_ND, nine-hole peg test nondominant hand; PASAT, Paced Auditory Serial Addition Test; WEIMuS, Würzburger Fatigue Inventory for MS.

Table 4. Correlations.

	EDSS	CGI	9HPT_D	9HPT_ND	PASAT	CES-D	EQ-5D	WEIMuS Cognitive	WEIMuS Physical
9HPT_D	−0.009	0.035	1.000						
9HPT_ND	−0.177	−.175	0.130	1.000					
PASAT	−0.041	0.014	0.082	−0.076	1.000				
CES-D	−0.005	−0.204	−0.113	−0.057	−0.137	1.000			
EQ-5D	−0.013	0.169	0.016	−0.070	−0.015	0.151	1.000		
WEIMuS Cognitive	−0.156	−0.133	0.089	0.095	−0.062	0.130	−.056	1.000	
WEIMuS Physical	−0.118	−0.069	−0.075	0.134	−0.192	0.208*	−0.044	0.582**	1.000

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).
Variables are the difference between timepoint 2 and timepoint 1 (Kendall's tau b).
CES-D, Center for Epidemiologic Studies depression scale; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQoL five dimensions questionnaire; 9HPT_D, nine-hole peg test dominant hand; 9HPT_ND, nine-hole peg test nondominant hand; PASAT, Paced Auditory Serial Addition Test; WEIMuS, Würzburger Fatigue Inventory for MS.

Table 5. MCID.

	MCID[a]			<MCID			p[b]
	N	Baseline	2 weeks	N	Baseline	2 weeks	
9HPT_D	40	39.80 ± 18.36	30.61 ± 10.72	147	32.77 ± 14.10	32.49 ± 13.03	<0.001
9HPT_ND	23	45.78 ± 21.44	34.39 ± 12.60	160	35.26 ± 21.35	35.01 ± 16.29	<0.001
EQ-5D	70	0.61 ± 0.27	0.83 ± 0.18	115	0.76 ± 0.17	0.73 ± 0.19	<0.001
WEIMuS Cognitive	96	12.74 ± 7.98	6.21 ± 6.47	82	12.50 ± 8.20	13.87 ± 8.64	<0.001
WEIMuS Physical	100	17.77 ± 6.51	10.27 ± 6.59	88	16.50 ± 8.52	18.76 ± 7.20	<.001
CES-D	93	17.84 ± 8.57	11.25 ± 6.28	93	13.13 ± 8.30	16.57 ± 9.29	<.001
PASAT	43	36.72 ± 13.09	46.77 ± 12.30	141	47.72 ± 10.66	46.57 ± 11.83	<0.001

[a]According to each test's MCID definition; see the methods section.
[b]Student's *t*-test considering score difference between 2 weeks and baseline of each MCID subgroup.
CES-D, Center for Epidemiologic Studies depression scale; EQ-5D, EuroQoL five dimensions questionnaire; MCID, minimal clinically important difference; 9HPT_D, nine-hole peg test dominant hand; 9HPT_ND, nine-hole peg test nondominant hand; PASAT, Paced Auditory Serial Addition Test; WEIMuS, Würzburger Fatigue Inventory for MS.

MS patients in the mild disability group were younger and had a shorter disease course than participants in other disability groups, which is explained by natural disease course, with more disability accumulating during disease evolution years, as has been described previously,[1] and this is expected to have an effect on hand dexterity performance and QoL. Further, RRMS patients had a lower disability and shorter disease course than patients with other diagnoses.

Whereas disability and diagnosis did not have a significant effect on the performance of most tests, patients with moderate disability had greater improvement than those with severe disability in dominant hand dexterity, and patients with

SPMS had a greater cognitive score improvement than those with PPMS. It has been reported previously that patients with greater disability also show greater upper limb impairment.[3] A study analyzing cognition in different MS subtypes, did not find significant differences in performance in the PASAT between individuals with either SPMS or PPMS.[33]

Patients above the MCID in each test, as described above, comprised a lower proportion of participants as those in the RFs group, as the latter group was defined according to their walking response. The greatest proportion of participants above the MCID threshold were in the cognitive and physical sections of the WEIMuS (50.79% and 52.91%, respectively). Once again, fatigue showed the greatest score improvement.

RFs performed better at 2 weeks when compared with the general sample in both sections of the WEIMuS, CES-D, and QoL, and with the dominant hand in the 9HPT, but not better in hand dexterity with the nondominant hand or the PASAT. As stated above, QoL, upper limb function and fatigue were expected to show the greatest improvement in RFs, as the available evidence suggests.[12,13,18] Fatigue was also the category with the greatest improvement in this subgroup. In contrast, NRF failed to show any significant improvement after 2 weeks, except for the PASAT ($p = 0.002$). Although there was not a significant correlation between most of the tests with each other or with disability, depressive symptoms correlated significantly with physical fatigue. Depression and fatigue in MS patients have been described to be closely related to each other[34] and it has even been suggested that they may share some physiopathological aspects.[34,35] As expected, participants exceeding the respective MCID showed significantly better performances than participants with performances below the respective MCID. Patients with improvements above the respective MCID also presented similar performance estimates compared with those in the RF subgroup.[22]

The early clinical trials performed by Goodman and colleagues exploring the effects of fampridine on participants with MS, focused on evaluating speed changes over time,[8–10] and proving fampridine as effective in improving walking speed in these participants. A large number of studies evaluating walking response to fampridine have focused on measuring speed and endurance changes over time[8–11,36], whereas some others have demonstrated improvement in QoL, fatigue, and arm function as secondary outcomes.[12,13,18] To date little experience has been generated on studies evaluating effects of fampridine besides changes in walking speed as the primary outcome. Although information is scarce, current information favors a positive effect of fampridine on fatigue, QoL, depression, and hand dexterity. Evidence is increasing in favor of a positive effect of fampridine on fatigue and this outcome must be further analyzed in larger trials with a universally accepted assessment procedure.

Our data suggests that patients benefiting from fampridine in walking parameters show positive improvement in hand dexterity, depressive symptoms, fatigue, and QoL, especially those patients with significant deficits in those domains. Criteria for determining response to fampridine based on physician's global judgement might be appropriate for determining response to that drug in patients with MS in other areas besides walking parameters. Relying on the MCID in each test might also provide a valid threshold for deciding nonwalking response to fampridine, although the lower proportion of participants in the MCID subgroup in comparison with the RFs warrants further investigation of different threshold scores.

The small changes seen in some of the tests could be due to a placebo effect of the drug on those functional outcomes, such as the nondominant upper limb motor tests and the PASAT. As the tests were performed 2 weeks apart, learning might have an effect on performance in the 9HPT, also considering that roughly one-half of the sample did not have a motor deficit in the upper extremities. Information provided by other studies was obtained using different outcome measures to those presented in this study, therefore this data should be used with caution when analyzing other studies with different outcomes.[37] The CES-D is a tool for screening for depressive symptoms, which is not a synonym of depression and this must be taken into consideration when analyzing studies reporting outcomes for depression.

As data from this study is derived from another trial, which used walking criteria for defining response to fampridine, the division of our population into RFs and NRFs could not be appropriate for determining the subgroup of participants with the greatest response to fampridine in nonwalking outcomes. A methodological limitation of the present study is the missing control group.

Conclusion

The current study can provide new information on the usefulness of fampridine treatment in the real-world setting and suggests that effects of this drug on RF patients in walking parameters extend to nonwalking functional outcomes. Considering the limitations posed by our study design, we provide evidence that physician's global judgement of walking improvement is a reliable measure for determining response to fampridine in nonwalking parameters. The greatest performance improvement was seen in physical and cognitive fatigue after 2 weeks (25.69% and 29.81%, respectively). The role of MCID of selected tests in determining response to fampridine must be further evaluated.

Acknowledgements

The main author would like to thank Consejo Nacional de Ciencia y Tecnología (CONACyT) for providing student scholarship during the months in which the writing of this article took place.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Katja Akgün has received personal compensation for oral presentation from Novartis, Bayer, and Biogen Idec. Undine Proschmann has received travel support from Novartis and Biogen Idec. Tjalf Ziemssen has received personal compensation for consultation and speaking fee as well as grant support by Biogen, Bayer, Celgene, Merck, Novartis, Sanofi, Teva, and Roche and is section editor for *BMC Neurology*. Francisco Alejandro Rodriguez-Leal, Rocco Haase, Judith Christina Eisele, Thorsten Schultheiss, and Raimar Kern have no conflicting interests to declare.

References

1. Kister I, Chamot E, Salter AR, *et al.* Disability in multiple sclerosis: a reference for patients and clinicians. *Neurology* 2013; 80: 1018–1024.
2. Ziemssen T. Multiple sclerosis beyond EDSS: depression and fatigue. *J Neurol Sci* 2009; 277(Suppl. 1): 37–41.
3. Kister I, Bacon T, Chamot E, *et al.* Natural history of multiple sclerosis symptoms. *Int J MS Care* 2013; 15: 146–158.
4. Murphy N, Confavreux C, Haas J, *et al.* Quality of life in multiple sclerosis in France, Germany, and the United Kingdom. Cost of Multiple Sclerosis Study Group. *J Neurol Neurosurg Psychiatry* 1998; 65: 660–666.
5. Nortvedt M, Riise T, Myhr K, *et al.* Quality of life in multiple sclerosis: measuring the disease effects more broadly. *Neurology* 1999; 53: 1098–1103.
6. Amato M, Ponziani G, Rossi F, *et al.* Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Mult Scler* 2001; 7: 340–344.
7. Rothwell P, McDowell Z, Wong C, *et al.* Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ.* 1997; 314: 1580–1583.
8. Goodman A, Brown T, Cohen J, *et al.* Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology* 2008; 71: 1134–1141.
9. Goodman A, Brown T, Edwards K, *et al.* A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010; 68: 494–502.
10. Goodman A, Brown T, Krupp L, *et al.* Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet* 2009; 373: 732–738.
11. Goodman A, Cohen J, Cross A, *et al.* Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study. *Mult Scler* 2007; 13: 357–368.
12. Allart E, Benoit A, Blanchard-Dauphin A, *et al.* Sustained-released fampridine in multiple sclerosis: effects on gait parameters, arm function, fatigue, and quality of life. *J Neurol* 2015; 262: 1936–1945.
13. Pavsic K, Pelicon K, Ledinek A, *et al.* Short-term impact of fampridine on motor and cognitive functions, mood and quality of life among multiple sclerosis patients. *Clin Neurol Neurosurg* 2015; 139: 35–40.

14. Prugger M and Berger T. Assessing the long-term clinical benefit of prolonged-release fampridine tablets in a real-world setting: a review of 67 cases. *Patient Relat Outcome Meas* 2013; 4: 75–85.
15. Ruck T, Bittner S, Simon O, *et al*. Long-term effects of dalfampridine in patients with multiple sclerosis. *J Neurol Sci* 2014; 337: 18–24.
16. Jensen H, Nielsen J, Ravnborg M, *et al*. Effect of slow release-Fampridine on muscle strength, rate of force development, functional capacity and cognitive function in an enriched population of MS patients. A randomized, double blind, placebo controlled study. *Mult Scler Relat Disord* 2016; 10: 137–144.
17. Rossini P, Pasqualetti P, Pozzilli C, *et al*. Fatigue in progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine. *Mult Scler* 2001; 7: 354–358.
18. Jensen H, Ravnborg M, Mamoei S, *et al*. Changes in cognition, arm function and lower body function after slow-release Fampridine treatment. *Mult Scler* 2014; 20: 1872–1880.
19. Morrow S, Rosehart H and Johnson A. The effect of Fampridine-SR on cognitive fatigue in a randomized double-blind crossover trial in patients with MS. *Mult Scler Relat Disord* 2017:4–9.
20. Ziemssen T, Hillert J and Butzkueven H. The importance of collecting structured clinical information on multiple sclerosis. *BMC Medicine* 2016; 14(1): 81. DOI: 10.1186/s12916-016-0627-1.
21. Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQoL Group. *Ann Med* 2001; 33: 337–343.
22. Rodriguez-Leal F, Haase R, Thomas K, *et al*. Fampridine response in MS patients with gait impairment in a real world setting: need for new response criteria? *Mult Scler* 2018; 24: 1337–1346.
23. European Medicines Agency. European public assessment report (EPAR) for Fampyra, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002097/WC500109958.pdf (2011) (accessed on 4 March 2019)
24. Busner J and Tarqum S. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)* 2007; 4: 28–37.
25. Fischer JS, Rudick RA and Cutter GR. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Mult Scler* 1999; 5: 244–250.
26. Greiner W, Claes C, Busschbach J, *et al*. Validating the EQ-5D with time trade off for the German population. *Eur J Health Econ* 2005; 6: 124–130.
27. Flachenecker P, Müller G, König H, *et al*. "Fatigue" in multiple sclerosis. Development and validation of the "Würzburger Fatigue Inventory for MS". *Nervenarzt* 2006; 77: 165–166, 168–170, 172–174.
28. Radlof L. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1997; 1: 385–401.
29. Hautzinger M, Bailer M, Hofmeister D, *et al*. Allgemeine depressionsskala (ADS). *Psych Praxis* 2012; 39: 302–304.
30. Kim S, Kim S, Jo M, *et al*. Estimation of minimally important differences in the EQ-5D and the SF-6D indices and their utility in stroke. *Health Qual Life Outcome*s 2015; 13: 32.
31. Jensen H, Mamoei S, Ravnborg M, *et al*. Distribution-based estimates of minimum clinically important difference in cognition, arm function and lower body function after slow-release fampridine treatment of patients with multiple sclerosis. *Mult Scler Relat Disord* 2016; 7: 58–60.
32. Sagawa Y, Magnin E, Paillot L, *et al*. Fampridine and quality of life in individuals with multiple sclerosis. *SpringerPlus* 2016; 5: 1070.
33. Potagas C, Giogkaraki E, Koutsis G, *et al*. Cognitive impairment in different MS subtypes and clinically isolated syndromes. *J Neurol Sci* 2008; 267: 100–106.
34. Bakshi R, Shaikh Z, Miletich R, *et al*. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult Scler* 2000; 6: 181–185.
35. Gobbi C, Rocca M, Pagani E, *et al*. Forceps minor and co-occurrence of depression and fatigue in multiple sclerosis. *Mult Scler* 2014; 20: 1633–1640.
36. Lo A, Ruiz J, Koenig C, *et al*. Effects of dalfampridine on multi-dimensional aspects of gait and dexterity in multiple sclerosis among timed walk responders and non-responders. *J Neurolog Sci* 2015; 356: 77–82.
37. Albrecht P, Bjørnå IK, Brassat D, et al. Prolongedrelease fampridine in multiple sclerosis: clinical data and real-world experience. Report of an expert meeting. *Therapeutic Advances in Neurological Disorders* 2018; 11. DOI: 10.1177/1756286418803248.