ARTICLE CLASS OF EVIDENCE

Effect of dalfampridine on information processing speed impairment in multiple sclerosis

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Abstract

Objective
To test a possible benefit of dalfampridine on information processing speed (IPS), a key function for cognitive impairment (CogIm) in multiple sclerosis (MS).

Methods
In this randomized, double-blind, placebo-controlled trial, we included patients with a score on the Symbol Digit Modalities Test (SDMT) under the 10th percentile of the reference value. Patients were randomized in a 2:1 ratio to receive dalfampridine 10 mg or placebo twice daily for 12 weeks. They underwent a comprehensive neuropsychological evaluation at screening (T0), at the end of treatment (T1), and after a 4-week follow-up (T2). The primary endpoint was improvement in SDMT.

Results
Out of 208 patients screened, 120 were randomized to receive either dalfampridine (n = 80) or placebo (n = 40). At T1, the dalfampridine group presented an increase of SDMT scores vs placebo group (mean change 9.9 [95% confidence interval (CI) 8.5–11.4] vs 5.2 [95% CI 2.8–7.6], $p = 0.0018$; $d = 0.60$ for raw score; and 0.8 [95% CI 0.6–1] vs 0.3 [95% CI 0.0–0.5], $p = 0.0013$; $d = 0.61$ for z scores; by linear mixed model with robust standard error). The improvement was not sustained at T2. A beneficial effect of dalfampridine was observed in the Paced Auditory Serial Addition Test and in cognitive fatigue.

Conclusion
Dalfampridine could be considered as an effective treatment option for IPS impairment in MS.

Trial registration
2013-002558-64 EU Clinical Trials Register.

Classification of evidence
This study provides Class I evidence that for patients with MS with low scores on the SDMT, dalfampridine improves IPS.

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Glossary

9-HPT = 9-Hole Peg Test; **25FWT** = Timed 25-Foot Walk Test; **BDI** = Beck Depression Inventory; **BRB-N** = Rao Brief Repeatable Battery of Neuropsychological Tests; **CI** = confidence interval; **CogIm** = cognitive impairment; **DMT** = disease-modifying treatment; **IPS** = information processing speed; **MFIS** = Modified Fatigue Impact Scale; **MS** = multiple sclerosis; **MSFC** = Multiple Sclerosis Functional Composite; **MSIS29** = Multiple Sclerosis Impact Scale; **PASAT-2** = Paced Auditory Serial Addition Test, 2 seconds rate; **PASAT-3** = Paced Auditory Serial Addition Test, 3 seconds rate; **SDMT** = Symbol Digit Modalities Test; **SPART** = Spatial Recall Test; **SRT-CLTR** = Selective Reminding Test–Consistent Long-Term Retrieval; **SRT-D** = Selective Reminding Test–Delayed Recall; **SRT-LTS** = Selective Reminding Test–Long-Term Storage; **ST** = Stroop Test; **TOW** = Tower of London test; **WLG** = Word List Generation.

Cognitive impairment (CogIm) is a disabling symptom of multiple sclerosis (MS) with deleterious consequences on employment, social functioning, and quality of life.[1,2] Information processing speed (IPS) has been proposed as a key deficit for CogIm and the first cognitive deficit to emerge in MS.[3,4]

The effectiveness of pharmacologic interventions for cognitive impairment in MS is unclear.[5] Several disease-modifying treatments (DMTs) are likely to benefit cognition, while the symptomatic treatment of it is unsatisfactory.[5]

Aminopyridines are broad-spectrum potassium (K+) channel blocking agents, with the capacity to improve conduction across demyelinated internodes in axons of the CNS.[6] In 2009, a randomized controlled trial demonstrated that the oral slow-release dalfampridine (Ampyra) is more effective than placebo in ameliorating walking speed as measured by the Timed 25-Foot Walk Test (25FWT).[7]

Both open-label studies[8–12] and randomized controlled studies[13–15] have tested the effects of dalfampridine on cognitive deficit in MS, reporting conflicting results. However, neuropsychological performances were not the primary endpoints in the randomized controlled trials[13,14] and patients were not selected according to the presence of CogIm.[13–15] Here, we present findings from our randomized, double-blind, placebo-controlled trial evaluating the effects of dalfampridine on cognitive function in patients with MS. The patients were selected for having a deficit in IPS. We defined the main outcome measure as the Symbol Digit Modalities Test (SDMT), which recently emerged as a possible outcome measure for trials on CogIm in MS.[16,17]

Methods

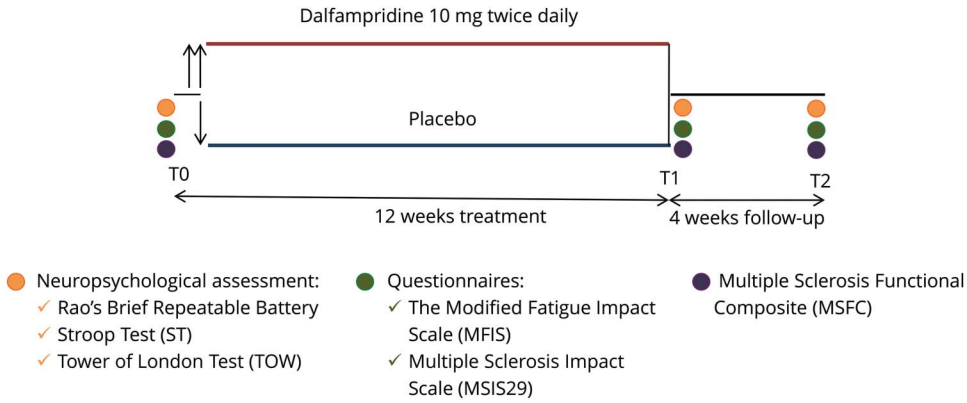
Primary research question

Is dalfampridine effective for the symptomatic treatment of CogIm in MS? This study provides Class I evidence that for patients with MS with low scores on the SDMT, dalfampridine improves IPS.

Study design and treatment

This was a randomized, double-blind, placebo-controlled trial. Figure 1 shows study design. Patients were screened during routine visits at the MS centers; after the verification of all inclusion and exclusion criteria, patients completed the screening procedures with the SDMT with the psychologist. Eligible patients completed the whole cognitive battery, the clinical evaluation, and other study questionnaires according to the study protocol (see below). At the same visit (T0), eligible patients were randomly assigned to take slow-release dalfampridine (10 mg twice daily) or placebo (tablets twice daily) in a 2:1 ratio for 12 consecutive weeks. Both groups

Figure 1 Trial design



were instructed to contact their physicians in case of any adverse events. After 12 weeks (T1), patients come back to the center to repeat the cognitive battery and behavioral tests and fill out the questionnaires. Physicians checked adherence to treatment, defined as percentage of tablets assumed of the number of those prescribed. All the evaluations were repeated after 4 weeks of washout period (T2).

Standard protocol approvals, registrations, and participant consents

The trial was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, Good Clinical Practice, and applicable regulatory requirements. The protocol was approved by the local ethics committee and all patients signed informed consent prior to any study procedure and registered on EU Clinical Trials Register with the number 2013-002558-64.

Participants

We enrolled patients from 2 regional referral MS centers in Rome from February 2015 to June 2016. Patients were referred to the trial in the clinics, based on cognitive complaints. Eligible participants were patients with a diagnosis of MS according to the revised McDonald criteria,[18] with an age ranging from 18 to 65 years (inclusive) and a score on the SDMT below the 10th percentile of normative values of the Italian population.[19,20]

Exclusion criteria were as follows:

1. Clinical relapse in the previous 60 days
2. History of major depression or psychosis
3. Severe or moderate depression according to Beck Depression Inventory–II (BDI) (with a cutoff score of 19)[21,22]
4. History of seizures
5. Any condition that would interfere with study conduction
6. Introduction or modification of any medication including medication for mood, fatigue, or cognition in the previous month

Randomization and blinding

At T0, an investigator (F.G.) not involved in any other study procedure was responsible for the randomization, performed with computer-generated random numbers in blocks of 9, and for drug assignment. Packages and tablets of dalfampridine and placebo were prepared from a separate organization at a separate site; they were identical and each package was identified only with a code. The correspondence between the codes and the treatment groups was saved in a closed envelope that was opened only at the end of the trial. The investigator responsible for randomization was also blind to demographic and clinical data of the patient (except for name and surname initials and years of birth). A 2-physician (treating and assessing) model was used to assist with study masking. At each site, the treating physician was responsible for selecting patients, performing the neurologic examination at screening, recording and managing adverse events, and monitoring safety assessments. The assessing physician was exclusively responsible for all neuropsychological assessments; all the evaluations (except for the neurologic examination) were performed by the same trained psychologist (F.D.L., 8 years of experience). Both the treating and the assessing physicians were blinded to treatment arms; the assessing physician was also blinded to all the adverse events that occurred during the study period.

Study endpoints

The main endpoint of efficacy–response to treatment was an improvement in the SDMT. The test consists of the presentation of a series of 9 symbols, each of which is paired with a single digit, labeled 1–9, in a key at the top of a sheet. The remainder of the page has a pseudorandomized sequence of the symbols and the participant must respond with the digit associated with each of these as quickly as possible. The score is the number of correct answers in 90 seconds. SDMT was administered orally. The administration of SDMT was preceded by a learning sequence at all timepoints; furthermore, to reduce the learning effect, 2 alternative versions of the test were presented (patients underwent form A at T0 and T2 and form B at T1).[19,23]

As secondary endpoints, we considered the improvement in the other cognitive tests of the Rao[24] Brief Repeatable Battery of Neuropsychological Tests (BRB-N), including the following:

1. Paced Auditory Serial Addition Test, 3 seconds rate (PASAT-3) and Paced Auditory Serial Addition Test, 2 seconds rate (PASAT-2) for concentration, sustained attention, and IPS in the auditory and verbal sphere
2. Selective Reminding Test–Long-Term Storage (SRT-LTS), Selective Reminding Test–Consistent Long-Term Retrieval (SRT-CLTR), and Selective Reminding Test–Delayed Recall (SRT-D) for verbal memory acquisition and delayed recall
3. 10/36 Spatial Recall Test (10/36-SPART) and the 10/36-SPART-delayed recall (10/36-SPART-D) for visuospatial memory acquisition and delayed recall
4. Word List Generation (WLG) for verbal fluency on semantic stimulus

Finally, the Stroop Test (ST) and the Tower of London test (TOW) were used for the assessment of executive function.[25,26]

To measure impairment in the single domains, for each cognitive test, we calculated the z score to quantify the number of SDs below the normative mean; we calculated the corrected score for each participant considering age and education as previously described,[19] then we applied the formula z score = (corrected score − population mean)/SD, based on the normative data of the Italian population.[19,27]

To quantify the degree of impairment in the individual patients at baseline, we calculated the Cognitive Impaired Index; a grading system was applied to each patient's score on each cognitive test of the BRB-N, depending on the number of SD below the normative mean.[27]

The tertiary outcomes of the study included the following:

1. The 9-Hole Peg Test (9-HPT) and the 25FWT that together with PASAT-3 seconds rate served to calculate the Multiple Sclerosis Functional Composite (MSFC) score were administered at the 3 time points.[28]
2. The Modified Fatigue Impact Scale (MFIS) was also administered at T0 and T1 to provide an assessment of the effects of fatigue in terms of physical, cognitive, and psychosocial functioning.[29]
3. Multiple Sclerosis Impact Scale (MSIS29) was used to measure the impact of disease on daily life.[30]

Statistical methods

Data management and analyses were performed by an independent research organization (GB Pharma Services & Consulting Srl, Pavia, Italy) with no role in the study design and data collection.

Based on works with timed ambulation metrics and supported by previous experience,[31,32] we assumed a 20% increase of the SDMT score over each participant baseline score as clinically relevant. On this basis, a total sample of 105 (70 active group, 35 placebo) patients was required to ensure a power of 80% (2-sided α level of 5%), therefore a total of 123 patients were expected to be enrolled, allowing for a dropout rate of 15%. The dropout rate was calculated using a previous pharmacologic trial on cognitive impairment in MS, reporting a drug discontinuation rate between 15% and 13%.[33,34]

Statistical analyses were performed using STATA 14.2 (StataCorp, College Station, TX). Two-tailed p values < 0.05 were considered as significant. The analysis was performed within the intention-to-treat population, defined as all randomized patients who took at least one drug dose.

At baseline, the number of patients with mild depression and fatigue was calculated in each study group considering a cutoff of 14 for BDI and a cutoff of 38 for MFIS.[21,29] The number of cognitively impaired patients in each group was calculated, defining as CogIm failure on at least 2 tests, and defining failure on a test as a score below 1.5 SD of normative data for the Italian population for the BRB-N and an equivalent score below 1 for ST and TOW.[19,25,26]

Between groups, differences in baseline clinical, demographic, and cognitive data were tested with χ^2 test for categorical variables and unpaired t test for continuous variables.

The primary endpoint was an improvement in the SDMT; linear mixed model with Huber-White robust standard error was used to evaluate SDMT performance over time considering patients as a random effect and the group as a fixed effect.

Missing data were input by multiple imputation, which uses a regression-based procedure to generate multiple copies of the data set, each of which contains different estimates of the missing values. We used the data augmentation algorithm in STATA 14.1 (mi command) to generate 10 imputed datasets. The imputation process of variables used in the analysis was based on time, group, and phenotype variables.

The same analysis was performed for both raw and z scores. The mean differences from T0 value and between T2 and T1 values and the relative confidence intervals (CIs) were obtained by estimating the marginal averages of the above models. The Cohen d effect size was also calculated; the effect sizes were rated as small, medium, and large for d of 0.2, 0.5, and 0.8, respectively. The percentage variation on the raw SDMT scores between T1 and T0 was calculated with the formula $[(T1 - T0)/(T0)] \times 100$ and percentage variations have been reclassified into 2 groups: below 20% and equal to or greater than 20%. Recently, the change of 3–4 points in the SDMT has been proposed as a sensitive measure for clinically meaningful change in cognitive performance[17,35]; therefore we calculated the number of patients presenting at least an improvement of 4 points in the raw SDMT scores between T1 and T0 in the 2 groups.

Missing data, variation of over 20%, and variation of at least 4 points were input by multiple imputation using a logistic regression–based procedure to generate multiple copies of the data set, each of which contains different estimates of the missing values.

Linear mixed model with robust standard error was also used for the evaluation of secondary and tertiary endpoints. Differences between treatment groups in outcome measures were tested considering patients as a random effect and the group as a fixed effect. Percentage improvement on the 25FWT was compared at T1 by means of an unpaired t test.

Finally, to exclude the possible confounding effect of fatigue, linear mixed model with Huber-White robust standard error was used to evaluate SDMT performance over time (categorical variable) considering patients as a random effect and the group as a fixed effect and adjusting for MFIS values (time-dependent variable).

We also performed secondary analysis considering the effect of disease phenotype in the whole sample and the effect only in patients with relapsing-remitting phenotype; data are reported in the supplementary material.

Data availability

Any data not published within this article will be publicly available at EU Clinical Trials Register with the identifier 2013-002558-64. Individual participant data will not be shared.

Results

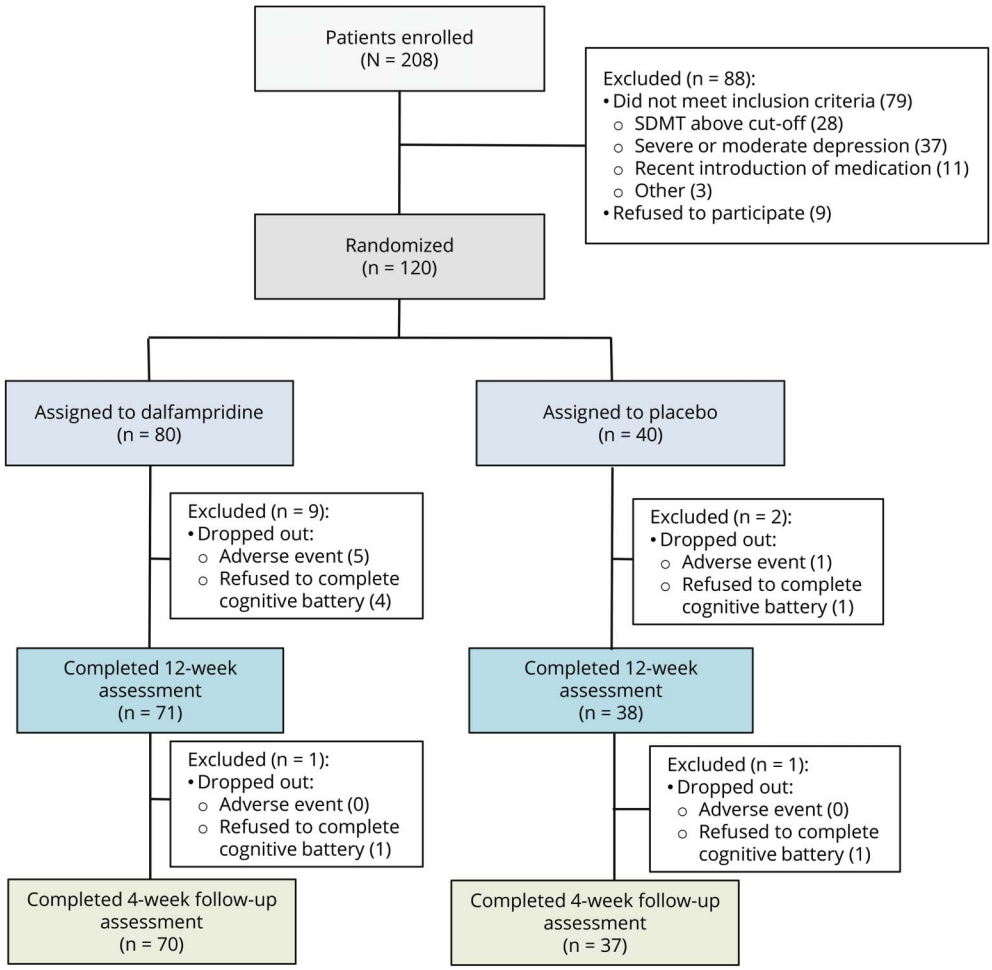
Out of 208 patients screened, 88 were excluded and 120 were randomized to receive dalfampridine (n = 80) or placebo (n = 40) (figure 2 shows patient dispositions). Seventy-one patients allocated to the dalfampridine group completed the 12 weeks of treatment while 9 patients were lost to follow-up: 5 of them presented an adverse event; the other 4 refused to complete the cognitive assessment at T1. Another patient refused to complete the 4-week follow-up assessment (T2); therefore, 70 patients in the dalfampridine group completed the study. Thirty-eight patients in the placebo group completed the 12 weeks of treatment; 1 presented an adverse event and 1 refused to complete the cognitive assessment at T1. Another patient from the same group refused to complete the cognitive assessment at T2; therefore, 37 patients in the placebo group completed the study.

The study population consisted of 74 women and 46 men, with a mean (SD) age of 48 (8.2) years, a mean (SD) instruction level of 13 (3.4) years, a mean (SD) time from disease onset of 16 (9) years, and a median Expanded Disability Status Scale score of 4 (ranging from 1 to 6). A total of 69 patients were under DMT; all of them had been on a stable regimen for at least 6 months. None of them presented a history of traumatic brain injury or learning disability or any other condition that could have influenced cognitive performance. Clinical and cognitive characteristics were balanced across groups (table 1). There were more patients with progressive disease in the placebo group (22.5%) than the treatment group (10.0%); however, the difference was not significant.

Dropout rate was lower than expected (10.8%); in patients who completed the study, adherence to study medication was more than 97% for both groups. We did not observe any relapses during the follow-up.

Data from all randomized patients were included in the analysis. Figure 3 summarizes the main outcome results. At the 12-week assessment (T1), we found a difference between groups in the SDMT raw score increase with an average change from a baseline of 9.9 (95% CI 8.5–11.4) for patients treated with dalfampridine and of 5.2 (95% CI 2.8–7.6) for

Figure 2 Consolidated Standards of Reporting Trials (CONSORT) flow diagram



SDMT = Symbol Digit Modalities Test.

Table 1 Baseline characteristics of treatment groups

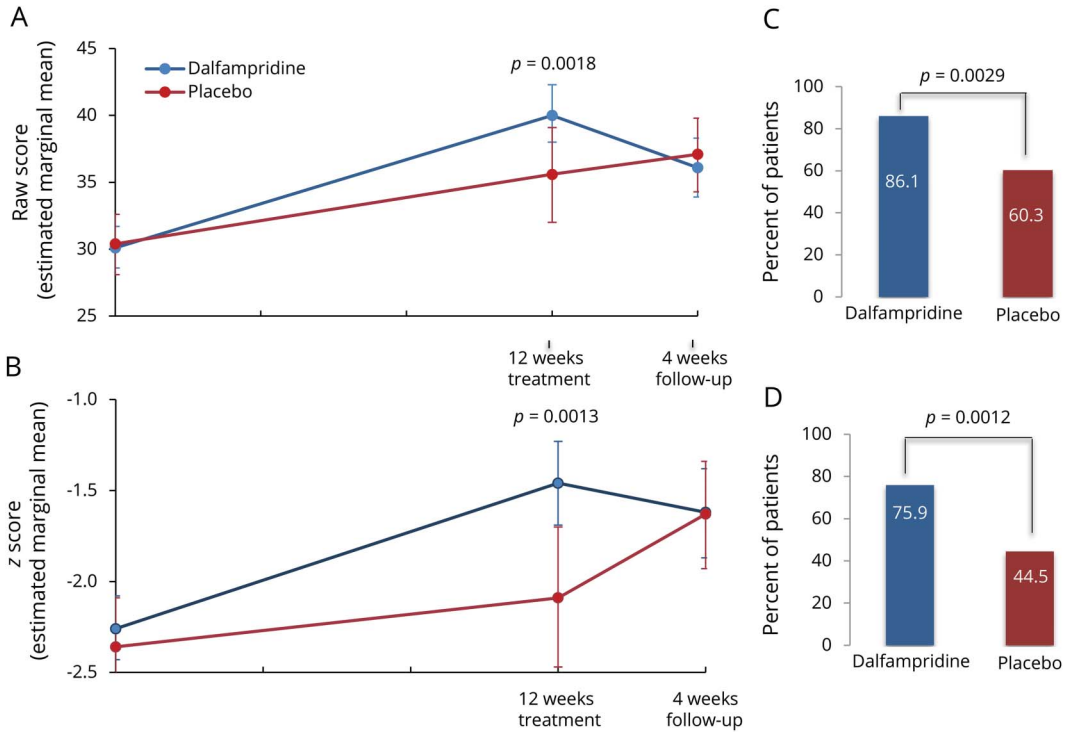
	Dalfampridine (n = 80)	Placebo (n = 40)
Age, y	49.3 ± 78	46.7 ± 8.7
Sex (% female)	50 (62)	24 (60)
Education, y	12.8 ± 3.5	14.1 ± 3.1
Disease duration, y	14.7 ± 9.0	17.2 ± 8.5
EDSS score	4 (1–6)	4.5 (1.5–5.5)
Phenotype		
Relapsing-remitting	72 (90)	31 (77.5)
Secondary progressive	7 (8.75)	7 (17.5)
Primary progressive	1 (1.25)	2 (5)
Patients under DMT	44 (55)	25 (62.5)
BDI score	10.70 (5.5)	12.27 (5.8)
Mildly depressed patients	30 (37.5)	20 (50)
MFIS score	19.8 (9.6)	21.7 (8.1)
Fatigued patients	46 (57.5)	26 (65)
No. of patients with CogIm	71 (88.8)	37 (92.5)
CII	18.3 (5.7)	18.6 (5.9)
SDMT		
Raw score	30.1 (7.2)	30.4 (7.4)
***z* Score**	−2.3 (0.8)	−2.4 (0.9)
PASAT-3		
Raw score	28.5 (12.6)	29 (12.4)
***z* Score**	−1.6 (1.2)	−1.8 (1.3)
PASAT-2		
Raw score	20.5 (10.7)	19.7 (10.2)
***z* Score**	−1.4 (0.9)	−1.6 (1)
SRT-LTS		
Raw score	29.7 (14.4)	31.7 (12.2)
***z* Score**	−1.4 (1.1)	−1.4 (1)
SRT-CLTR		
Raw score	19.6 (14.6)	21.1 (11.7)
***z* Score**	−1.5 (1)	−1.5 (0.9)
SRT-D		
Raw score	5.5 (2.6)	6.0 (2.7)
***z* Score**	−1.6 (1.1)	−1.5 (0.9)
SPART		
Raw score	13.3 (5.2)	13.4 (5.3)
***z* Score**	−1.6 (1.1)	−1.7 (1.1)
SPARTD		
Raw score	4.5 (2)	4.7 (2.4)
***z* Score**	−1.1 (0.9)	−1.1 (1)
WLG		
Raw score	20.7 (5.9)	20.2 (6.4)
***z* Score**	−1.2 (1)	−1.3 (1.1)
TOW	28.7 (5.1)	27.7 (5.9)
ST	20.5 (8.3)	19.7 (10.2)
MSIS29 score	73.9 (26.4)	76.2 (22.8)
MSFC score	0.2 (2)	−0.2 (2.6)
25FWT	7.3 (2.4)	8.2 (4.9)
9-HPT		
Dominant hand	26.2 (11.3)	29.4 (15.4)
Nondominant hand	28 (9.8)	31.5 (17.1)

Abbreviations: 9-HPT = 9-Hole Peg Test; 25FWT = Timed 25-Foot Walk Test; BDI = Beck Depression Inventory; CII = Cognitive Impairment Index; CogIm = Cognitive Impairment; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; MFIS = Modified Fatigue Impact Scale; MSFC = Multiple Sclerosis Functional Composite; MSIS29 = Multiple Sclerosis Impact Scale; PASAT-2 = Paced Auditory Serial Addition Test, 2 seconds rate; PASAT-3 = Paced Auditory Serial Addition Test, 3 seconds rate; SDMT = Symbol Digit Modalities Test; SPARTD = 10/36 Spatial Recall Test–Delayed Recall; SPART = 10/36 Spatial Recall Test; SRT-CLTR = Selective Reminding Test–Consistent Long-Term Retrieval; SRT-D = Selective Reminding Test–Delayed Recall; SRT-LTS = Selective Reminding Test–Long-Term Storage; ST = Stroop Test; TOW = Tower of London Test; WLG = Word List Generation.
Data are reported as mean (SE) or n (%), except for EDSS score, which is expressed as median (range). Raw score for all cognitive tests are reported; *z* scores are reported for tests belonging to the Rao Brief Repeatable Battery.

patients in the placebo group ($p = 0.0018$) showing a medium effect size ($d = 0.60$). We obtained a difference between groups also in the improvement of SDMT *z* score with an average change from a baseline of 0.8 (95% CI 0.6–1.0) for patients treated with dalfampridine and of 0.3 (95% CI −0.0 to 0.5) for patients in the placebo group ($p = 0.0013$, $d = 0.61$). At 4 weeks follow-up (T2), the difference between the groups was no longer significant (figure 3, A and B). The proportion of patients with an improvement of at least 4 points in the SDMT raw score and with an improvement of at least 20% in the SDMT was also higher in the group treated with dalfampridine compared to placebo (86.1% vs 60.3% [$p = 0.0029$] and 75.9% vs 44.5% [$p = 0.0012$]) (figure 3, C and D).

Table 2 shows mean raw scores for all cognitive tests (secondary efficacy outcomes) at T0 and T1 according to study group. We did not find an effect of the drug on tests assessing executive functions (ST and TOW) or on tests assessing

Figure 3 Main outcome



The main outcome of the study was an improvement on Symbol Digit Modalities Test (SDMT). We show (A) raw scores at the 3 time points in treated patients and in the placebo group; (B) *z* scores at the 3 time points in treated patients and in the placebo group. *z* Scores are based on normative data; (C) the percentage of patients presenting an increased raw score of at least 4 points in raw scores; and (D) the percentage of patients presenting an increased raw score (≥20%). *p* in (A) and (B) express differences between groups in score changes calculated by linear mixed model with robust standard error; *p* in (C) and (D) express differences between groups calculated with χ^2 test.

verbal and spatial memory (SRT-LTS, SRT-CLTR, SRT-D, SPART) and verbal fluency (WLG). We found an effect of dalfampridine on the other cognitive tests assessing processing speed, working memory, and attention: the average improvement of PASAT-3 *z* score was 0.6 (95% CI 0.3–0.9) for patients treated with dalfampridine and 0.1 (95% CI −0.2 to 0.5) for patients in the placebo group ($p = 0.0327$, d = 0.39); for PASAT-2 z score the average improvement was 0.6 (95% CI 0.4–0.8) for patients treated with dalfampridine and 0.2 (95% CI −0.1 to 0.5) for patients in the placebo group ($p = 0.0319$, $d = 0.40$).

With regard to the tertiary endpoints, we found an improvement of the MSFC total score, which was sustained from the improvement on the PASAT (table 2).

The evaluation of fatigue with the MFIS demonstrated a positive effect of the drug on fatigue. Mean improvement on MFIS total score was −7.84 (95% CI −11.7 to −3.9) in the dalfampridine group compared with −0.2 (95% CI −4.6 to 4.9) in the placebo group ($p = 0.0085$, $d = -0.47$). In the cognitive subscale, we found a mean improvement of 4.6 (95% CI −6.5 to −2.8) in the dalfampridine group compared with 0.2 (95% CI −2.1 to 2.5) in the placebo group ($p = 0.0009$, $d = -0.60$). The difference between groups in the physical and psychological subscale did not reach statistical significance (−2.6 [95% CI −4.8 to −0.4] vs −0.2 [95% CI −2.5 to 2.1] physical subscale and −0.58 [95% CI −1.1 to −0.02] vs 0.18 [95% CI −0.6 to 1.0] in the psychological subscale, respectively) (figure 4).

When we adjusted the mixed model on SMDT data by MFIS total score, the mean change at T1 remained higher in dalfampridine compared with placebo considering both raw and *z* scores (9.7 [95% CI 8.3–11.1] vs 4.9 [95% CI 2.6–7.2], $p = 0.0008$, and 0.8 [95% CI 0.6–1.0] vs 0.2 [95% CI 0.0–0.5], $p = 0.0005$, respectively).

We could not demonstrate an effect in improving daily life measured considering the MSIS29 total score.

Tables S1 and S2 (doi.org/10.5061/dryad.sd32fh5) show results of secondary analysis performed adjusting for disease phenotype and restricting the analysis to the relapsing-remitting group.

Table 3 summarizes the adverse events according to study group. Adverse events leading to discontinuation in the dalfampridine group were postural instability (2 patients), sleeplessness (1 patient), focal seizure (1 patient), palpitation, and postural instability (1 patient); 1 patient in the placebo group discontinued the study because of postural instability

Table 2 Study measures

			Difference dalfampridine vs placebo at T1		Difference dalfampridine vs placebo at T2
			p Value		*p* Value
	T0 marginal, mean (SE)	T1 marginal, mean (SE)	Effect size	T2 marginal, mean (SE)	Effect size
Primary endpoint, SDMT					
Raw score					
Dalfampridine	30.1 (0.8)	39.8 (1.1)	0.0018[a]	36.1 (1.1)	0.6208
Placebo	30.4 (1.2)	35.6 (1.8)	0.60[a]	37.1 (1.4)	−0.09
***z* Score**					
Dalfampridine	−2.3 (0.1)	−1.5 (0.1)	0.0013[a]	−1.6 (0.1)	0.5729
Placebo	−2.4 (0.1)	−2.1 (0.2)	0.61[a]	−1.6 (0.2)	−0.09
4 points increase, n (%)					
Dalfampridine	—	86.1	0.0029[a]		
Placebo	—	60.3	—		
20% increase, n (%)					
Dalfampridine	—	75.9	0.0012[a]		
Placebo	—	44.5	—		
Secondary endpoints					
PASAT-3					
Dalfampridine	28.5 (1.4)	35.9 (1.4)	0.0365[a]	33.5 (1.6)	0.1710
Placebo	29.0 (1.9)	31.9 (2.1)	0.42[a]	31.0 (2.3)	0.25
PASAT-2					
Dalfampridine	20.5 (1.2)	27.6 (1.3)	0.1258	25.3 (1.4)	0.9744
Placebo	19.7 (1.6)	23.9 (1.8)	0.29	24.4 (2.0)	0.01
SRT-LTS					
Dalfampridine	29.7 (1.6)	31.7 (1.9)	0.7452	34.6 (1.6)	0.7643
Placebo	34.6 (1.8)	35.7 (2.1)	0.06	35.9 (2.0)	0.05

Continued

Table 2 Study measures *(continued)*

	T0 marginal, mean (SE)	T1 marginal, mean (SE)	Difference dalfampridine vs placebo at T1	T2 marginal, mean (SE)	Difference dalfampridine vs placebo at T2
			p Value		*p* Value
			Effect size		Effect size
SRT-CLTR					
Dalfampridine	19.6 (1.6)	24.4 (1.8)	0.4724	24.1 (1.6)	0.4141
Placebo	21.1 (1.8)	24.3 (1.9)	0.12	23.7 (2.0)	0.17
SRT-D					
Dalfampridine	5.5 (0.3)	6.6 (0.3)	0.2266	6.3 (0.3)	0.7375
Placebo	6.0 (0.4)	6.5 (0.4)	0.22	6.5 (0.5)	0.77
SPART					
Dalfampridine	13.3 (0.6)	15.6 (0.6)	0.0679	14.9 (0.6)	0.5233
Placebo	13.4 (0.8)	13.3 (1.0)	0.37	14.4 (0.9)	0.13
SPARTD					
Dalfampridine	4.5 (0.2)	5.5 (0.3)	0.1512	5.1 (0.3)	0.7852
Placebo	4.7 (0.4)	4.9 (0.3)	0.26	5.3 (0.4)	−0.06
WLG					
Dalfampridine	20.7 (0.7)	23.5 (0.9)	0.5635	22.7 (0.8)	0.9467
Placebo	20.2 (1.0)	22.2 (1.0)	0.11	22.3 (1.1)	−0.02
TOW					
Dalfampridine	28.7 (0.6)	27.3 (0.5)	0.0505	28.3 (0.5)	0.4635
Placebo	27.7 (0.9)	28.2 (0.9)	−0.40	27.9 (0.8)	−0.15
ST					
Dalfampridine	20.5 (0.9)	21.3 (0.8)	0.8225	21.7 (1.0)	0.8750
Placebo	19.3 (1.3)	19.9 (1.1)	0.04	20.3 (1.3)	0.03

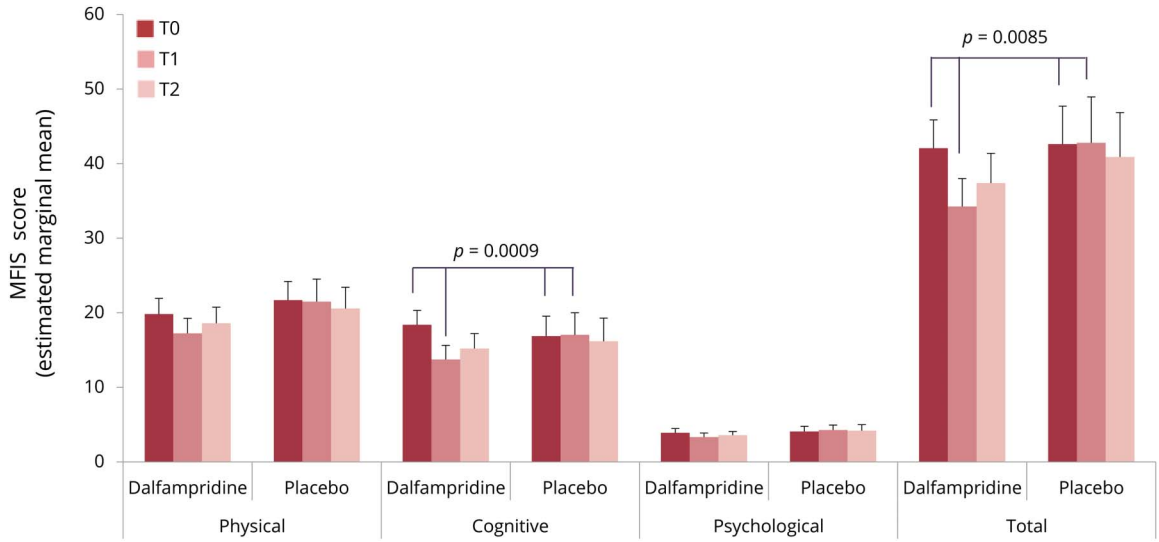
Continued

Table 2 Study measures *(continued)*

	T0 marginal, mean (SE)	T1 marginal, mean (SE)	Difference dalfampridine vs placebo at T1	T2 marginal, mean (SE)	Difference dalfampridine vs placebo at T2
			p Value		*p* Value
			Effect size		Effect size
Tertiary endpoints					
MSIS29					
Dalfampridine	73.7 (3.0)	68.0 (3.1)	0.8731	70.5 (3.0)	0.8801
Placebo	76.2 (3.6)	71.3 (3.5)	−0.03	73.7 (3.7)	−0.03
MSFC					
Dalfampridine	0.1 (0.2)	0.6 (0.3)	0.0302[a]	0.7 (0.3)	0.2344
Placebo	−0.2 (0.4)	−0.5 (0.5)	0.42[a]	−0.1 (0.4)	0.24
MSFC components					
PASAT-3					
Dalfampridine	28.5 (1.4)	35.9 (1.4)	0.0365[a]	33.5 (1.6)	0.1710
Placebo	29.0 (1.9)	31.9 (2.1)	0.42[a]	31.0 (2.3)	0.25
25FWT					
Dalfampridine	7.4 (0.30)	6.5 (0.4)	0.3320	7.1 (0.4)	0.9096
Placebo	8.3 (0.8)	8.0 (0.7)	−0.55	8.1 (0.8)	−0.02
Dominant hand, 9-HPT					
Dalfampridine	26.2 (1.27)	25.0 (1.5)	0.5030	25.7 (1.3)	0.7726
Placebo	29.4 (2.43)	26.8 (1.6)	0.13	28.3 (1.7)	0.07
Nondominant Hand, 9-HPT					
Dalfampridine	28.0 (1.10)	26.7 (1.1)	0.4219	27.5 (1.4)	0.6683
Placebo	31.5 (2.68)	31.5 (3.0)	−0.17	31.6 (2.9)	−0.07

Abbreviations: 9-HPT = 9-Hole Peg Test; 25FWT = Timed 25-Foot Walk Test; MSFC = Multiple Sclerosis Functional Composite; MSIS29 = Multiple Sclerosis Impact Scale; PASAT-2 = Paced Auditory Serial Addition Test, 2 seconds rate; PASAT-3 = Paced Auditory Serial Addition Test, 3 seconds rate; SDMT = Symbol Digit Modalities Test; SPART = 10/36 Spatial Recall Test; SPARTD = 10/36 Spatial Recall Test–Delayed Recall; SRT-CLTR = Selective Reminding Test–Consistent Long-Term Retrieval; SRT-D = Selective Reminding Test–Delayed Recall; SRT-LTS = Selective Reminding Test–Long-Term Storage; ST = Stroop Test; TOW = Tower of London Test; WLG = Word List Generation. *p* Values for continuous variables refer to linear mixed model with robust standard error; *p* values for categorical variables refer to χ^2 test. For secondary outcomes we report raw scores; data on *z* scores are reported in the text.
[a] Values reaching statistical significance.

Figure 4 Modified Fatigue Impact Scale (MFIS) scores according to study groups and study periods



Total scores and physical, cognitive, and psychosocial functioning subscales are reported. *p* Values express differences between groups in score changes calculated by linear mixed model with robust standard error; error bars represent upper level of 95% confidence interval.

with a consequent fall. The focal seizure and the fall were considered as a serious adverse event since they resulted in a brief visit to the emergency department even if no long-term consequence was reported. The focal seizure was considered as possibly related to the drug. No other serious adverse events were observed.

Table 3 A dverse events (AEs) reported during the study

	Dalfampridine (n = 80)	Placebo (n = 40)
Patients with any AE	64 (80)	28 (70)
Patients with mild AEs	62 (77.5)	28 (70)
Patients with moderate AEs	4 (0.5)	0 (0)
Patients with severe AEs	1 (1)	1 (2.5)
Serious AEs	1	1
Possibly or probably treatment-related serious AEs	1 (1)	0
Most frequent AEs[a]		
Spasticity	11 (14)	19 (47.5)
Insomnia	9 (11)	1 (2.5)
Mood alteration	9 (11)	3 (7.5)
Urinary tract infection	7 (9)	4 (10)
Balance disorder	6 (7.5)	5 (12.5)
Dizziness	6 (7.5)	2 (5)
Headache	6 (7.5)	4 (10)
Asthenia	4 (5)	6 (15)
Fall	4 (5)	2 (5)
Gastric pain	4 (5)	4 (10)

We report number (%) of patients with AEs and the number of most frequent AEs (Common Terminology Criteria for Adverse Events 4).
[a] Occurring in more than 5% of one treatment arm.

Discussion

Our study suggests the effectiveness of dalfampridine in improving IPS and working memory in patients with MS with impairment in IPS. Until recently, no drugs had been proved to be effective for the symptomatic treatment of CogIm in MS[6]; therefore our results may be considered as relevant in the care of patients with this disabling symptom. Primary outcome analysis of the trial showed a greater improvement of cognitive performance in dalfampridine-treated patients compared with the placebo group; we found also that the effect size of the treatment was medium, suggesting a moderate practical effect of the drug. The improvement in cognitive function was not present after a month of drug interruption; this is in line with the proposed mechanism of action—the improvement of conduction in demyelinated pathways via blockade of voltage-dependent potassium channels—which makes the effects of dalfampridine rapid and reversible.

A crucial point in such a trial is the definition of the response to treatment. A recent review on this matter defined a change in the test score of 4 points as clinically meaningful.[17] However, these data refer to negative changes associated with relapses or values predictive of unemployment rather than improvement associated with effective treatment.[17] Nevertheless, we found a difference close to 5 points between the marginal means in dalfampridine vs placebo (table 2). Therefore, our results seem encouraging, although further studies, with a specific design, are needed to correctly define the number of patients who would benefit from treatment and to clarify the methodology by which they should be identified.

We also demonstrated a greater proportion of patients with an improvement in SDMT score of least 20% in the treated group vs placebo (67.5% vs 42.5%). When considering cognitive improvement, we need to take into account possible testing effects, a robust cognitive phenomenon by which retrieval practice on a test actually improves subsequent memory more than either massed or spaced restudy. As expected, due to this phenomenon, we found several patients with an improvement above 20% also in the placebo group.

Analysis of the secondary outcome measures confirmed the positive effect of the drug on IPS and on working memory, showing an effect on PASAT-2 and PASAT-3. We could not demonstrate an effect in other cognitive domains. IPS represents the key deficit underlying cognitive dysfunction in MS.[3,4] However, impairment in IPS is not always associated with deficits in other domains that are classically considered to be related to IPS[36] and conversely, impairment of learning and memory is observed even in patients without a comorbid deficit in IPS.[2,3] Recent findings suggest that CogIm may result from the damage of several brain regions and that different damage locations may lead to different characteristics of deficit.[37,38] However, if we could speculate that the effect of the dalfampridine on brain structures may result in a specific benefit on processing speed, this hypothesis contrasts with previous reports showing a beneficial effect of the drug on verbal fluencies.[11,15] An alternative explanation to consider is that patient selection affected the lack of a positive result: as mentioned above, the inclusion criteria required a deficit in IPS whereas the impairment in other domains was not necessary. In our population, compared with SDMT, mean scores for other tests were distanced in a lower grade from the values expected for healthy population; therefore the improvement in this test may have been less evident due to a ceiling effect.

We failed to confirm the effectiveness of dalfampridine on lower limb function as previously repored.[9,13,39] However, we showed an improvement in the 25FWT in treated patients. The lack of statistical significance is probably due to the study design, which was powered to detect cognitive changes rather than motor improvement. We failed also to confirm a positive effect on the 9-HPT as previously reported.[8] However, the lack of effect could be related to a lack of dynamic range or sensitivity of the test, rather than a lack of effectiveness of the drug.

Our study showed a positive effect of the drug on fatigue, with a more pronounced beneficial effect on the cognitive subscale. These data confirm previous observations[10,15] and suggest that the drug should also be considered as suitable treatment for this disabling and common symptom of MS.

We did not observe a positive effect of the drug on daily life measured with the MSIS29 total score. These data apparently contrast with the beneficial effect previously reported from other studies.[40,41] The short duration of our trial could have limited the recognition of a positive effect.

With regard to safety considerations, as expected, some adverse events including postural instability, insomnia, and dizziness were reported more frequently in the active arm than in the placebo group. The majority of adverse events, however, were mild. The number of reported events was comparable with literature data except for a slight increase in the frequency of insomnia, headache, and balance disorder.[7]

As mentioned above, a limitation of the present study was the short duration of the treatment that did not allow us to assess the long-term effects of the drug. Recently, Broicher et al.[15] demonstrated persisting beneficial effect of dalfampridine on different aspects of cognition and fatigue over a period of 2 years.

Our study demonstrates the effectiveness of dalfampridine in improving IPS in patients with MS with impairment in the SDMT and confirms that the safety profile of the drug is in line with published data.[7]

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