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Effects of fampridine on cognition and upper limb mobility in patients with Multiple Sclerosis.

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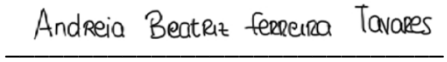
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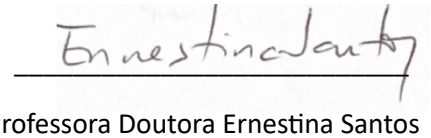
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O coorientador,



Dr. João Paulo Araújo de Moura

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Dedication

À minha família,

Aos meus amigos,

Por serem colo e casa,

Por acreditarem, quando só existem dúvidas,

Pelo apoio e paciência inesgotáveis,

Por tornarem este caminho tão mais leve e feliz,

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Resumo

Introdução: A esclerose múltipla é a doença desmielinizante crónica do sistema nervoso central mais comum, sendo uma das principais causas de incapacidade neurológica em adultos jovens. A seguir à nevrite ótica, a incapacidade para a marcha é uma das primeiras manifestações, sendo, por isso, considerada um indicador primário de progressão da doença. A fampridina, um bloqueador dos canais de potássio de alta voltagem, embora com indicação formal somente para melhorar a marcha, tem apresentado resultados discrepantes quanto aos seus efeitos na cognição e na função dos membros superiores em doentes com esclerose múltipla .

Objetivo: Este estudo teve como objetivo avaliar o impacto da Fampridina na cognição e na mobilidade dos membros superiores, em doentes que respondem em termos de marcha, durante um período de 6 meses.

Métodos: Foi realizado um estudo retrospetivo longitudinal, unicêntrico, aberto, não controlado e não randomizado em doentes com esclerose múltipla tratados com Fampridina, num hospital terciário de referência. Foram utilizadas várias escalas para avaliar o efeito da fampridina, entre as quais, Timed 25-Foot Walk (T25FW) para avaliar a velocidade da marcha, Multiple Sclerosis Walking Scale 12 (MSWS-12) para uma avaliação subjetiva feita pelo próprio, o Mini Mental State Examination (MMSE) e o Symbol Digit Modalities Test (SDMT) ambos para avaliar a função cognitiva e, por fim, o Nine-Hole Peg Test (9HPT) para avaliar a função dos membros superiores. Todos os dados foram analisados estaticamente, incluindo regressões lineares com Generalized Estimating Equations (GEE) para avaliar os efeitos ao longo do tempo, nos diferentes testes.

Resultados/Discussão: Dos 178 pacientes identificados, 59 foram incluídos no estudo. A fampridina demonstrou melhorias significativas na velocidade de marcha, particularmente em doentes com fenótipos progressivos da doença, com Expanded Disability Status Scale (EDSS) mais baixos e níveis de escolaridade mais elevados ($p < 0.001$). No entanto, os seus efeitos na cognição e na função dos membros superiores permanecem ambíguos (MMSE $p=0.362$; SDMT $p=0.498$; 9HPT $p=0.159$). As características *baseline* dos doentes, como EDSS, nível de escolaridade e subtipo da doença influenciam significativamente a resposta ao tratamento. A avaliação subjetiva, feita pelo próprio, através do MSWS-12 desempenha um papel importante na avaliação da eficácia da fampridina e na compreensão da progressão da doença.

Conclusão: Embora a fampridina se mostre promissora na melhoria da marcha, os seus efeitos na cognição e na função dos membros superiores em doentes com EM permanecem ambíguos. São necessários mais estudos para elucidar o seu potencial terapêutico e otimizar estratégias de tratamento para pacientes com esclerose múltipla.

Palavras- Chave: Esclerose Múltipla, Fampridina, Cognição, Membros Superiores

Abstract

Background: Multiple sclerosis (MS) is the most common chronic demyelinating disorder of the nervous system, being one of the main causes of neurological disability in young adults. Following optic neuritis, walking disability is one of the first clinical manifestations, serving as a primary indicator of disease progression. Fampridine, a high-voltage potassium channel blocker, is primarily indicated for improving gait. However, its effects on cognition and upper limb function in MS patients have shown conflicting results.

Objective: This study aims to assess the impact of Fampridine on cognition and upper limb mobility in patients with Multiple Sclerosis who respond to Fampridine in gait parameters, over 6 months.

Methods: This is a longitudinal, monocentric, open-label, uncontrolled, and non-randomized study involving MS patients treated with Fampridine at a tertiary referral hospital. Various scales were used including Timed 25-Foot Walk (T25FW) to assess walking speed, Multiple Sclerosis Walking Scale 12 (MSWS-12) to assess self-reported walking ability, Mini Mental State Examination (MMSE), and Symbol Digit Modalities Test (SDMT) both to assess cognitive function and The Nine-Hole Peg Test (9HPT) to evaluate upper limb function. Statistical analyses, including linear regressions with generalized estimating equations, were performed to assess the effects over time on outcome measures.

Results/Discussion: Of the 178 identified patients, 59 were included in the study. Fampridine demonstrated significant improvements in walking speed, particularly in patients with progressive MS phenotypes, with lower disability scores and higher education levels ($p < 0.001$). However, its effects on cognition and upper limb function in MS patients remain ambiguous (MMSE $p=0.362$; SDMT $p=0.498$; 9HPT $p=0.159$). Patient characteristics such as EDSS, education level, and disease subtype significantly influence treatment response. Patient-reported outcomes also play an important role in evaluating the efficacy of fampridine and understanding the progression of the disease

Conclusion: The improvement in gait provided by fampridine was not accompanied by upper limb function and cognition in the 6 months following treatment initiation. Further research is warranted to unravel its therapeutic potential.

Keywords: Multiple Sclerosis, Fampridine, Cognition, Upper Limb

List of Abbreviations

9HPT - The Nine-Hole Peg Test

CNS - Central Nervous System

DMT - Disease Modifying Treatment

EAN - European Academy of Neurology

ECTRIMS - European Committee for Treatment and Research in Multiple Sclerosis

EDSS - Expanded Disability Status Scale

FS – Functional System

GEE - Generalized Estimating Equations

MMSE – Mini-Mental State Examination

MS - Multiple Sclerosis

MSWS-12 - Multiple Sclerosis Walking Scale

PASAT - Paced Auditory Serial Addition Test

PPMS - Primary Progressive Multiple Sclerosis

PRFAM - Prolonged Release Fampridine

RRMS – Relapsing-Remitting Multiple Sclerosis

SD - Standard Deviation

SDMT - Symbol Digit Modalities

SPMS - Secondary Progressive Multiple Sclerosis

T25FW - Timed 25-Foot Walk

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Introduction

Multiple sclerosis (MS) is the most common chronic demyelinating disorder of the nervous system. It typically affects patients aged between 20 and 45 years, representing one of the leading causes of neurological disability in young adults[1]. The most common form of MS consists of periods of disease activity, called relapses, followed by periods of neurological stability (relapsing-remitting MS). Some patients have persistently increased neurological dysfunction, consisting of the progressive MS forms. These are associated with increased disability compared to relapsing-remitting MS, including cognitive impairment, which is more frequent and severe[2–4]. The pathophysiology of MS is not fully understood, with the most consistent pathological features of the disorder being inflammation, multifocal demyelination, and subsequent neuronal degeneration[5]

The diagnosis of MS follows the McDonald criteria, which focus on the dissemination in time and space of the disease, i.e., the appearance of new lesions over time and the presence of lesions in different regions of the central nervous system (CNS), which can be confirmed clinically and/or radiologically[6]. Walking disability is one of the most relevant clinical milestones and a primary indicator of disease progression [7]. Additionally, upper limb function and fine motor skills, balance, and cognition can also undergo significant changes during the disease[8]. Patients' cognition is affected regardless of the MS subtype and disease phase, with the most affected cognitive domains being information processing speed and memory, followed by attention, executive functioning, and verbal fluency[2,3,9].

Fampridine is a high-voltage potassium channel blocker that crosses the blood-brain barrier, promoting an improvement in the conduction of action potentials and synaptic and neuromuscular transmission of demyelinated neurons[1,7]. Although not a disease-modifying drug, i.e., not reducing the number of relapses, lesions, or degree of brain atrophy, it is considered the first-line symptomatic pharmacological treatment in patients with gait impairments[1,10]. Results of the ENHANCE study of prolonged-release fampridine (PRFAM) revealed significant improvements in walking in patients with a score between 4 and 7 on the Expanded Disability Status Scale (EDSS)[11–13] (Table I). In fact, with the use of this drug, patients have shown a substantial increase in walking speed, not only at the functional level but also in a subjective dimension, assessed according to the 12-item Multiple Sclerosis Walking Scale (MSWS-12)[1,12,14]. Thus, the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) have formally established that fampridine is appropriate for all patients with an EDSS between 4 and 7 who, after 15 days of treatment, show an improvement of between 15% and 25% on the T25FW scale.

Alongside these outcomes, some studies have questioned the drug's effect on other limitations of MS patients, notably upper limp mobility/function, and cognition. However, published results are scarce and conflicting, making this a relevant research point.

Objective

This study aims to assess the impact of Fampridine on cognition and upper limb mobility in patients with Multiple Sclerosis who respond to Fampridine in gait parameters.

Methods

Study Population

This was a retrospective longitudinal, monocentric, open-label, uncontrolled, and non-randomized study involving patients with MS followed at the neuroimmunology outpatient clinic from a tertiary referral hospital selected from an institutional database containing all MS cases followed since 2007. All patients were diagnosed with MS according to McDonald criteria[6]. This being a retrospective study, the decision to prescribe fampridine had already been taken prior by the attending neurologist, following the EAN and ECTRIMS recommendations[15]. Patients were included if they were considered responders to fampridine according to gait parameters, defined as an improvement of 15% to 25% on the T25FW scale at 15 days.[6] All included cases were receiving stable doses of any Disease Modifying Treatment (DMT) for at least 6 months before the beginning of fampridine treatment.

Study Design

All patients undergoing treatment with fampridine were subjected to the application of a set of scales before and 15 days after the start of treatment, to select those who are responders and therefore those who have a formal indication to maintain treatment. Participants were tested again after 3 and 6 months of treatment. Patients maintained the same DMT and physical rehabilitation program throughout the evaluations.

Scales

The following assessments were used to evaluate the impact of Fampridine: T25FW, MSWS-12, Mini Mental State Examination (MMSE), Symbol Digit Modalities Test (SDMT), and The Nine-Hole Peg Test (9HPT). Assessments were performed at baseline, after 2 weeks, and after 3 and 6 months of treatment with fampridine.

The Timed 25-Foot Walk (T25FW) is a standard method to evaluate the walking speed. Patients are considered responders when there is an improvement of 15% to 25% in the T25FW after 15 days[7,14].

The Multiple Sclerosis Walking Scale 12 (MSWS-12) is used to evaluate self-reported walking ability/limitations through 12 questions that address various aspects beyond speed walking, such as: climbing and descending stairs, balance, smoothness of gait, and the support, effort, and concentration required. Higher MSWS-12 scores indicate worse walking ability, with the desirable outcome being a decrease in self-reported limitations.

The Mini Mental State Examination (MMSE) grants a global, brief, systematic, and validated cognitive assessment. Results were interpreted according to the recommended cut-off scores per level of education, for the Portuguese population[16].

The Symbol Digit Modalities Test (SDMT) measures visual scanning, cognitive processing speed and memory, and has been used as a surrogate to screen for cognitive impairment in MS patients[17–19], once the most affected domains are lack of attention and memory and slow information processing.

The Nine-Hole Peg Test (9HPT) is a scale that assesses motor function and speed of upper limbs. The test consists of asking the patient to insert 9 pegs into holes and remove them afterwards, using dominant and then nondominant hand. The recorded time, in seconds, is measured before and after fampridine initiation with the desirable outcome being a decrease in the average execution time of the test[8,17,20].

Statistical Analysis

Descriptive statistics were used to describe demographic and disease related characteristics at baseline, as well as test scores at different timepoints. Categorical variables were summarized as absolute and relative frequency (%). Continuous variables were reported as mean and standard deviation (SD). An EDSS cut-off of 6, which defines the need for persistent gait support, was used to define two groups: those with mild-moderate disability (EDSS ≤ 6) and those with severe disability (EDSS > 6). Disease subtypes were dichotomized as progressive disease (i.e., primary progressive MS and secondary progressive MS) vs. relapsing–remitting (RRMS). For age, we established 2 subgroups: younger than 65, and 65 or more years of age. For educational level, the patients were divided into two groups: those with less than 9 years of education and those with 9 or more years of education. This threshold matches the mandatory education level in Portugal until 2010. Therefore, patients with 9 years of education or less were considered to have only the minimum compulsory education, labelled here as "low" education. Concerning DMT, treatment modalities were grouped in immunomodulators (i.e., Interferon beta, glatiramer acetate)[21], immunosuppressors (i.e., Sphingosine 1-phosphate receptor modulators, Monoclonal antibodies, Mitoxantrone)[21], both, or no DMT.

Linear regressions fitted with generalized estimating equations (GEE) were performed to verify the effects of time on outcome measures, while considering sex, age, education, EDSS, MS subtype, and simultaneous treatment, which were included in the linear model as covariates.

All collected data was statistically analyzed using the IBM SPSS Statistics 29.0.1.1 (Mac OS) with statistical significance set to $p<0.05$.

Ethical approval: This study was approved by the ethics committee of Centro Hospitalar Universitário de Santo António and Instituto Ciências Biomédicas Abel Salazar – Universidade Porto (N/ REF.ª 2023.256 (218-DEFI/208-CE))

Results

In total, 178 patients taking fampridine were identified. From this group, 119 were excluded for the following reasons: 29 were considered non-responders to fampridine in standard gait parameters (18 at 2 weeks assessment, 5 at 3 months evaluation and 6 at 6 months); 13 due to treatment suspension (7 at patient's initiative and 6 due to adverse events); and 77 were lost to follow-up/ non-adherence.

Fifty-nine patients were included in the study. Table II summarizes the baseline demographic and clinical characteristics.

Most patients were female (55.93%), and the mean age of patients was 55.81 (SD=9.72) years, with a mean age of disease diagnosis of 35.13 (SD=11.92). Most patients were below the age of 65 years (76.27%). The mean disease duration was 20.51 (SD=9.75) years. The most common MS phenotype was progressive (50.84%), 28.81% being primary progressive (PPMS) and 22.03% secondary progressive (SPMS). The median EDSS score was 5.50 (Interquartile: 4.50, 6.00), and most patients had an EDSS score ≤ 6 (81.36%). The mean number of years of education was 11.24 (SD=5.36). Concerning DMT, 33.90% were receiving immunomodulators, 22.03% immunosuppressors, 1.69% both, and 42.38% none. Adjusting the MMSE scores using the cutoffs recommended for the Portuguese population[16], 4 patients with 3 to 6 years of education have an MMSE score < 24, and 2 patients with 6 or more years of education have an MMSE score < 27, which amounts to 6 out of 59 patients meeting the criteria for mild cognitive impairment in this screening test.

All patients were evaluated with the selected scales at baseline, 2 weeks, and 3 months. At 6 months only 40 patients (67.8%) completed the evaluation. Table III summarizes the mean score at each time point.

Considering the T25FW, at week 2, there was an unadjusted improvement of 0.83 m/s in walking speed (Figure 2). Despite a slight decrease in absolute numbers in subsequent assessments, linear regressions fitted with GEE revealed a significant time effect ($p<0.001$), therefore, indicating a significant improvement in walking speed (Table IV).

The effect of time remained significant ($p<0.001$) when considering sex, age, education, EDSS, disease subtype, immunosuppressive therapy, and immunomodulator treatment as covariates (Table IV). Potential interactions between time and other independent variables on T25FW were explored in separate GEE analyses. Patients with higher education had more sustained gains on the T25FW than patients with lower education (time x education: $p=0.029$). Patients with EDSS score ≤ 6 have a higher gait speed at baseline and show a more pronounced improvement at 15 days compared to those with EDSS > 6 (time x EDSS: $p=0.022$) (Table V, Figure 3).

A significant interaction between time and disease subtype (p=0.044) was observed on T25FW. Patients with progressive phenotypes had lower scores at baseline and showed slightly greater gains from baseline at 15 days, but less sustained gains at subsequent follow-up points, compared to RRMS. In both phenotypes, it is noted that the benefits in gait are primarily obtained within the first 15 days. Over the 6-month evaluation period, the percentage of T25FW improvement diminishes, with patients maintaining a gait speed always superior to their baseline (Figure 4).

No significant interaction effect was observed between time x sex (p=0.934), time x age (p=0.146), time x immunosuppressive therapy (p=0.188), or time x immunomodulator therapy (p=0.297) on T25FW score (Table V).

Regarding MSWS-12 score, the effect of time remained statistically significant (p<0.001) when considering age, EDSS, disease subtype, immunosuppressive therapy, and immunomodulator treatment as covariates (Table IV). Potential interactions between time and other independent variables on MSWS-12 were explored in separate GEE analyses. A significant interaction was observed between time and disease subtype (p=0.004) (Table V). Patients with progressive MS phenotypes had higher MSWS-12 scores at baseline and greater benefit at 15 days compared to those with RR phenotype. At subsequent follow-ups, both phenotypes had similar scores on the MSWS-12.

There was a significant interaction between time and DMT type (p=0.012) on MSWS-12. Patients on immunosuppressors showed great reductions at 15 days and then had a progressive reduction of benefit on the subsequent follow-ups, whereas patients under immunomodulator treatment had better scores at baseline, smaller reductions at 15 days, and continuous benefit at 3 months and maintenance of those gains at 6 months.

No significant interactions were observed between time and variables sex (p=0.189), age (p=0.695), education (p=0.632), EDSS (p=0.500), and immunosuppressive therapy (p=0.552) (Table V).

Unadjusted means of MMSE and SDMT show a marginal improvement over the 6 months. The unadjusted mean value of MMSE increased from 28.17 to 28.71, representing an increase of 1.92%. Meanwhile, the unadjusted mean value of SDMT increased from 40.95 to 42.70, rising 4.27% (Table III). However, no significant effects of time were observed on MMSE (p=0.362) and SDMT (p=0.498), meaning that there is no significant variation over time in the SDMT and MMSE scores (Table IV).

For the 9HPT, at week 2 the unadjusted mean execution time of the test decreased by 1.7 seconds. However, at months 3 and 6, a slight increase in the total execution time was noted (Figure 5). No significant effect of time was observed on 9HPT ($p<0.159$) (Table IV).

Discussion

In this study, we found that the improvement in gait provided by fampridine was not accompanied by upper limb function and cognition in the 6 months following treatment initiation.

We discuss the results obtained in each of these parameters in detail in the following sections.

Cognition

There was no significant variation over time in the SDMT and MMSE scores, which aligns with most previously published studies that have failed to demonstrate effects of fampridine on cognitive function[22]. Pavsic, K., et al. (2015) failed to demonstrate either short or long-term impact of fampridine on cognitive function, obtaining a scarce 1.3% of average improvement (p=0.432)[22]. Their study used PASAT (Paced Auditory Serial Addition Test) to evaluate cognition, a sole measure of cognition in the Multiple Sclerosis Functional Composite (MSFC)[23]. While the SDMT emphasizes visual scanning and processing, PASAT primarily focuses on auditory processing and working memory as well as calculating ability. Despite assessing distinct cognitive functions, SDMT and PASAT both assess processing speed and attention, and fampridine appears unable to significantly improve either. Goodman et al. (2008), in a dose comparison trial of fampridine, didn't reveal a significant improvement of PASAT, as well[24]. Notably, in the study of Satchidanand et al. (2018), both PASAT and SDMT were used as cognitive parameters, with no effect of fampridine on either compared to placebo (PASAT p=0.441; SDMT p=0.395)[25]. In contrast to all the above, Jensen et al. (2014), using SDMT to evaluate cognition, showed significant improvement of cognitive function after 28 days of therapy. Nevertheless, they had a short period of follow-up, and a control group was lacking, introducing a possible placebo effect [17].

Since SDMT is based on visual scanning and processing, it relies upon several other functions such as visual acuity, which were not considered here. This omission could skew the results, as visual impairments can significantly impact cognitive test performance[18,26]. Thus, failure on SDMT may reflect impairment in visual processing besides mental processing speed. Davis et al (2009) demonstrated that simple measures of corrected visual acuity predicted more than 21% of the variance in a widely used neuropsychological test. This is relevant since MS patients are particularly prone to visual dysfunction due to lesions in the optic pathway.

Still regarding cognition, it is known that education is a protective factor for the development of cognitive dysfunction in MS and patients with a higher level of education sustain their cognitive status better than those with "low" education.[27]. Since our study population had a relatively high education level (mean years of education 11.24 ± 5.36) it may be that some of the expected

differences are dissipated. In parallel, another study that sought to demonstrate the effect of fampridine on cognitive fatigue also had a large highly educated cohort (mean years of education 13.4 ± 1.8), and also showed no cognitive benefit from fampridine[9]. The study by Jensen et al. (2014), which showed significant improvement of SDMT had no cognitive or educational assessment made at baseline.

Only a minority of our sample (6/59) met the criteria for Mild Cognitive Impairment according to the population-adjusted MMSE so the number of patients with cognitive impairment that could potentially benefit significantly from fampridine treatment was low, suggesting a possible "ceiling effect". In the future, a broader sample in terms of educational backgrounds and severities of cognitive impairment in which fampridine is used could provide useful information on this topic.

All the aforementioned studies are based on the principle that, since fampridine's mechanism of action enhances axonal conduction by blocking potassium channels along demyelinated axons, the treatment benefits might extend beyond walking ability alone, reaching other demyelinated areas. However, cognitive dysfunction in MS is mainly attributed to cortical grey matter changes and brain atrophy, rather than being caused by classic white matter lesions[28]. Demyelinating white matter lesions have little correlation with cognitive impairment in MS[29]. Likewise, the rationale for fampridine to improve cognitive symptoms may be questionable, which might explain our findings.

Upper Limb Mobility

9HPT was used to evaluate unilateral fine manual dexterity.[8,30] We found no significant improvement over time in this parameter. Similar findings were reported in other studies. Marion et al. (2020) conducted a double-blinded placebo-controlled trial with 40 patients with MS, with the primary outcome measure being the performance on the 9HPT at 4 weeks, and the persistence of effects at 8 weeks being the secondary endpoint. There was no significant difference observed between the drug and placebo at any time point. Similarly to our study, patients exhibited a wide variety of upper limb impairments [31]. It is reasonable to think that different impairments will have different treatment outcomes, making it challenging to evaluate benefits, especially in the setting of a small sample size that prevents a comprehensive subgroup analysis.

Savin et al. (2016) studied 26 patients with MS using not only 9HPT, but also hand grip, pinch strength, and activities of daily life. Fampridine increased dominant hand grip and pinch strength 1 month following treatment by 12% and 10% ($p<0.05$), respectively. 9HPT improved by 11.3% after 3 months of treatment ($p<0.05$), however below the threshold for the minimal clinically important difference (at least 20%)[30,31]. A distinction between this study and ours lies in the baseline evaluation, wherein Savin et al. meticulously analyzed upper limb impairments in each patient.

Although all participants in our study being evaluated at baseline with 9HPT, we did not verify whether all individuals exhibited a level of impairment that could potentially yield significant benefits from fampridine treatment. This absence of a minimum 9HPT score, in line with the published normative value for age, sex, and hand dominance[32], can be a contributing factor to the lack of a significant treatment effect. Establishing a baseline measure of upper limb dysfunction could mitigate the risk of a "ceiling effect" for improvement.

Additionally, arm and hand function relies upon several other functions such as tremor, which were not considered here [22]. Previous research has already demonstrated how these deficits, when present, can impact this test and its results[33,34]. A study demonstrated that there was a positive correlation between the score on a particular tremor rating scale (ADL-T24) and the 9HPT score, indicating that patients with more severe tremor will predictably require more time to complete the 9HPT, masking fampridine's therapeutic potential [34].

Bertoni et al. (2015) studied 105 patients with MS with heterogeneous EDSS scores and demonstrated a marked and significant decrease in the 9HPT within the severe non-ambulant group compared to the mild-disability group ($p<0.01$). When considering bilateral involvement, the prevalence increased from approximately 33% in patients with EDSS < 4 to nearly 91% in patients with EDSS scores exceeding 6.5. This indicates that manual dexterity tends to deteriorate with increasing disability[33,35] and impactful improvements in hand function may be attainable at higher EDSS levels. However, such improvements may be less discernible in study populations that do not include patients with significant hand dysfunction[35].

T25FW

Our study also showed that the improvement in the T25FW score was influenced by the EDSS, as patients with EDSS score ≤ 6 have a higher gait speed at baseline and experience greater benefits in the initial assessment, at 15 days, compared to those with EDSS > 6.

A study on fampridine-induced changes in gait kinetics showed that patients with the most significant benefits had higher EDSS scores[36], suggesting that individuals with higher levels of functional disability will demonstrate a greater response. This discrepancy in EDSS Influence can be explained by the heterogeneity of patients in this group. Some individuals with EDSS ≤ 6 might already experience other deficits such as ataxia, spasticity, paresis, sensory impairments, and nystagmus that impair walking[12,36,37]. This finding is reflected in the recent update of the EU label for PR-fampridine, advising physicians to evaluate clinical benefit not solely based on walking speed, but also based on walking ability[12]. The way patients walk is as important as their walking speed, and impairments may already be present at early disease stages.

Regarding education, our study showed that patients with higher education had more sustained gains on the T25FW than patients with lower education. This raises an important association between education, its protective effect on cognitive reserve, and motor functioning. As mentioned above, individuals with higher education levels often have greater cognitive reserve, which can help them better manage neurodegenerative conditions like multiple sclerosis[27]. On the other hand, patients with lower education may be more prone to develop cognitive dysfunction and, in association, greater motor disability[4]. This cognition-motor coupling has already been addressed in other studies [4,25,27,38]. Satchidanand et al. (2018) demonstrated that a positive response to fampridine in ambulation was linked to improvements in auditory processing speed and working memory, which suggests once more a cognitive-motor interaction. This interaction is crucial for complex motor tasks, such as walking in MS Patients, which requires more attention, coordination, balance, and timing than in the general population. This way, it is plausible to think that by leveraging cognitive reserve through tailored interventions, we can potentially enhance both cognitive and motor outcomes in patients with MS. Future research needs to delve deeper into the mechanisms behind this association and its implications for treatment strategies.

Concerning the MS subtype, results in this study also showed that walking improvements in patients with progressive MS phenotypes exceed those observed in patients with the RR course. The benefits in gait were mostly noticed in the 15 days assessment, but patients maintained their gains in gait through the 6 months of follow-up. This association with phenotypes has not been previously reported in the literature. This fact holds great clinical relevance: on one hand, evaluation at 2 weeks might translate into the maximum expected benefit from fampridine; on the other hand, it informs clinicians on the expected trajectory of improvement and may aid in the decision on whether to discontinue treatment. This finding warrants further investigation to confirm its reproducibility and to understand the underlying mechanisms, potentially guiding clinical decisions. It is important to emphasize that determining whether patients still benefit from fampridine is particularly challenging in those with a progressive phenotype, as progression may mask the benefits of fampridine[35].

When analyzing age as a covariate, significant effects of time ($p<0.001$) were identified. However, no interaction was found ($p=0.146$), indicating that age < 65, despite tending to present higher gait speed, does not exhibit any interaction with the gains induced by fampridine over time. This can be explained by the natural disease course. On one hand, younger patients have a shorter disease duration and therefore accumulate less disability over time, thus having better walking abilities. On the other hand, older patients accumulate more disability over the years as the disease progresses[20,39].

Likewise, there is an effect of time on sex, immunosuppressive therapy and immunomodulator therapy, but there is no interaction with the gains induced by fampridine over time.

MSWS-12

It is known that MSWS-12 provides a subjective assessment by the patient on their walking ability, inquiring about aspects of walking not captured by objective measurements, such as T25FW. Typically, a clinically meaningful improvement in MSWS-12 is defined as a mean score reduction of ≥ 8 points[8,12].

Regarding MSWS-12 score, the effect of time remained statistically significant ($p<0.001$) when considering EDSS, but no significant interaction was observed. Concerning disease subtype, we demonstrated a significant interaction between time and disease subtype ($p=0.004$), as patients with progressive MS phenotypes had higher MSWS-12 scores at baseline and greater gains at 15 days compared to those with RR phenotype. At subsequent follow-ups, both phenotypes had similar scores on the MSWS-12.

According to Albrecht et al (2018), the T25FW is moderate to strongly correlated with a self-reported walking disability on the MSWS-12[12]. Additionally, although no significant interaction with EDSS was observed in our study, some reports show that MSWS-12 is better related to the EDSS in the mild MS subgroup and in early stages of the disease than walking speed in the T25FWT[37]. This implies that the MSWS-12 can identify neurological impairments that are similarly captured by the EDSS, but not by objective walking assessments. Moreover, it suggests that this subjective tool may identify subtle and gradual deficits better than objective walking speed tests [12,37,40].

This way, it is reasonable to assume that MSWS-12 may have a significant role in capturing gait deficits longitudinally, over time. In progressive phenotypes, as symptoms of MS tend to manifest with varying rates of progression over time, there is a possibility that minor mobility impairments, particularly in individuals with mild disability, are more effectively identified through subjective complaints. This approach offers a comprehensive perspective on mobility challenges, compared to the assessment based exclusively on spatio-temporal parameters of gait. This might explain our findings, as patients with progressive MS phenotypes had higher MSWS-12 scores at baseline and greater gains at 15 days. Lerede et. al (2023) demonstrated that patient-reported outcomes exhibit sensitivity to future transitions to progressive subtypes, once individuals who transition to progression have higher patient-reported outcomes during their relapsing-remitting phase, compared to those who do not transition since onset (all $p< 0.001$)[41]. This way, these self-reported outcomes can detect early signs of progression in MS throughout the course of the disease and across different subtypes, thus establishing their validity as a tool for cost-effective, long-term

measurement of the physical decline of MS. Moreover, we know that the onset of physical disability occurs several years prior to the clinical identification of progressive subtypes. This finding suggests that incorporating such outcomes in routine clinical practice could improve early intervention strategies. Further research is needed to validate these findings and explore their practical implementation in monitoring MS progression.

The observed interaction between time and DMT type on the MSWS-12 might be explained by the differing mechanisms of immunosuppressors and immunomodulators. Disease-modifying drugs are effective in relapsing forms of MS and in initial inflammatory stages, but few treatments are effective for progressive forms of the disease[42].

Patients on immunosuppressors experienced significant improvements at 15 days. However, these benefits diminished over time, likely due to the continued progression of the underlying disease. In contrast, patients on immunomodulators had better baseline scores, suggesting a more stable disease course before the study. They showed continuous improvement at 3 months, sustaining it at 6 months, potentially due to an immune modulation that might promote long-term stability.

Immunosuppressors, alongside their cytotoxic properties, inhibit the immune response by targeting intracellular and cell-surface ligands, and diverse cytokines. Studies say that this widespread suppression of the immune system may be beneficial in patients with severe or rapidly worsening MS [21,42,43]. However, as B and T cells may play a role in remyelination, broad immunosuppression may reduce the efficiency of tissue repair following disease activity [21]. Immunomodulators, on the other hand, shift the immune balance from pro-inflammatory to anti-inflammatory responses, mediated through T_h2 cytokines (i.e. IL-4, IL-10) [43]. Neurotrophic factors, which regulate the survival and differentiation of nerve cells, also shift the central nervous system cytokine balance from T_h1 to T_h2. This way, selective immunomodulatory therapy might enhance the neuroprotective functions of autoimmune T cells and preserve/promote remyelination, leading to long-term stability and repair of neural pathways[21,42,43]. This long-term stability may be the explanation to our findings, as patients undergoing immunomodulators showed continuous and sustained improvement through the 6 months of follow-up. This pattern highlights the importance of considering the type of DMT when evaluating the effectiveness of fampridine in improving walking ability in MS patients.

Limitations

Due to the small sample size, the study may have been underpowered to detect small but clinically significant differences in outcomes, particularly in subgroups of patients with different

disease phenotypes or levels of disability. Additionally, it lacked blinding, which may introduce bias in the assessment of outcomes, particularly subjective measures such as patient-reported outcomes. Furthermore, the study's lack of a control group restricts the ability to compare the effects of fampridine with those of a placebo or standard care.

Future research in this area might also change inclusion criteria. Experts say that in the majority of patients with MS, it becomes evident within a 2-week timeframe whether a patient is responsive to PR-fampridine or not; however, certain patients may require an additional 2 weeks of treatment for confirmation[12]. This means that more patients could have been included if one more assessment had been conducted, specifically 1 month after the initiation of fampridine to reassess the response. Moreover, disease activity and clinical symptoms may advance, especially in those with progressive phenotypes, and in certain cases, the response to fampridine may evolve later in the disease course, despite an initial lack of response. This way, the follow-up duration of 6 months may not be sufficient to capture long-term effects of fampridine on gait, cognitive function, and upper limb mobility.

Noteworthy, further research is necessary to better understand the pathophysiologic differences in individuals who do and do not respond to fampridine.

Additionally, the maximum walking distance may offer a more precise and accurate functional measure compared to T25FW, as it is the distance rather than speed that sometimes limits patients in their daily activities and lives[44]. The reliance on solely objective measures such as T25FW and 9HPT might overlook the patient's subjective experience of mobility and quality of life, this way, it is important to incorporate patient-reported outcome measures, such as quality of life scales and symptom diaries, to capture the patient's perspective on treatment efficacy.

Addressing these limitations in future studies could enhance the validity and generalizability of findings related to the efficacy of fampridine in MS management.

Conclusion

In conclusion, in line with most previously published studies, fampridine showed promise in enhancing gait (i.e. walking speed), particularly in patients with progressive MS phenotypes and among those with lower disability scores and higher education levels. However, it did not demonstrate significant improvements in cognition or upper limb function, meaning that its effects on these domains remain uncertain.

Patient characteristics such as EDSS, education level and disease subtype significantly influence treatment response. Patient-reported outcomes also play an important role in evaluating the efficacy of fampridine and understanding the progression of the disease, emphasizing the need for personalized approaches in MS management.

Understanding these nuances is crucial for optimizing treatment strategies and managing expectations both for physicians and patients with MS undergoing fampridine therapy. Further research is warranted to unravel its therapeutic potential.

Appendix

Tables

Table I Expanded Expanded Disability Status Scale (EDSS) [13]

0	Examination shows everything is normal
1	No disability, minimal signs in one functional system (FS)
1.5	No disability, minimal signs in more than one FS
2	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in 2 functional system
3	Moderate disability in one FS, or mild disability in 3 FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting
6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting
7	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transfering. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10	Death due to MS

Table II Baseline demographics and clinical characterization

	n = 59
Sex, *n* (%)	
Female	33 (55.93)
Male	26 (44.07)
Age, years	
Mean (SD)	55.81 (9.72)
Range	37 - 78
Age < 65 *n* (%)	45 (76.27)
Age ≥ 65 n (%)	14 (23.73)
Laterality, *n* (%)	
One	56 (94.92)
Ambidextrous	2 (3.39)
Missing	1 (1.69)
Education, years	
Mean (SD)	11.24 (5.36)
Range	3 - 21
Age of MS diagnosis, years	
Mean (SD)	35.31 (11.92)
Range	12 - 61
Disease duration, years	
Mean (SD)	20.51 (9.75)
Range	6 - 46
MS phenotype, *n* (%)	
PPMS	17 (28.81)
SPMS	13 (22.03)
RRMS	29 (49.16)
EDSS score	
Median	5.50
Q1	4.50
Q3	6.00
Interquartile Range	1.50
EDSS ≤ 6, *n* (%)	48 (81.36)
EDSS > 6, *n* (%)	11 (18.64)
Current DMT, *n* (%)	
None	25 (42.38)
Immunomodulator	20 (33.90)
Imunossupressive	13 (22.03)
Both	1 (1.69)
Clinical relapses during the past year, *n* (%)	
None	48 (81.36)
One	10 (16.95)
Two	1 (1.69)
Imagiological relapses during the past year, *n* (%)	
None	55 (93.22)
One	3 (5.09)
Two	1 (1.69)

Table III Unadjusted mean of test results off treatment and after treatment (mean values ±SD)

	Baseline *n = 59*	Week 2 *n = 59*	Month 3 *n = 59*	Month 6 *n = 40*
T25FW	2.60 (± 1.48)	3.43 (± 1.57)	3.27 (± 1.58)	3.33 (± 1.85)
MSWS-12	71.94% (± 17.14)	59.55% (± 16.81)	58.58% (±16.37)	63.55% (± 19.49)
MMSE	28.17 (± 2.70)	28.25 (± 2.81)	28.27 (± 2.68)	28.71 (± 2.41)
SDMT	40.95 (± 16.45)	41.20 (± 16.57)	41.86 (± 16.60)	42.70 (± 17.39)
9-HPT	58.80 (± 23.20)	57.12 (± 20.20)	57.53 (± 17.67)	60.43 (± 21.18)

Table IV Time effect on different assessments using linear regressions fitted with GEE

	Time effect	Co-variates						
		Sex	Age	Education	EDSS	MS subtype	Imunossupressive DMT	Immunomodulator DMT
	p	*p*	*p*	*p*	*p*	*p*	*p*	*p*
T25FW	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
MSWS-12	**<0.001**		**<0.001**		**<0.001**	**<0.001**	**<0.001**	**<0.001**
MMSE	0.362							
SDMT	0.498							
9-HPT	0.159							

Table V Potential interactions between time and other independent variables on T25FW and MSWS-12 using linear regressions fitted with GEE

	Time effect	Sex x Time	Age x Time	Education x Time	EDSS x Time	MS Subtype x Time	Imunossupressive x Time	Immunomodulator x Time
	p	*p*	*p*	*p*	*p*	*p*	*p*	*p*
T25FW	**<0.001**	0.934	0.146	**0.029**	**0.022**	**0.044**	0.188	0.297
MSWS-12	**<0.001**	0.189	0.695	0.632	0.500	**0.004**	0.552	**0.012**

Figures

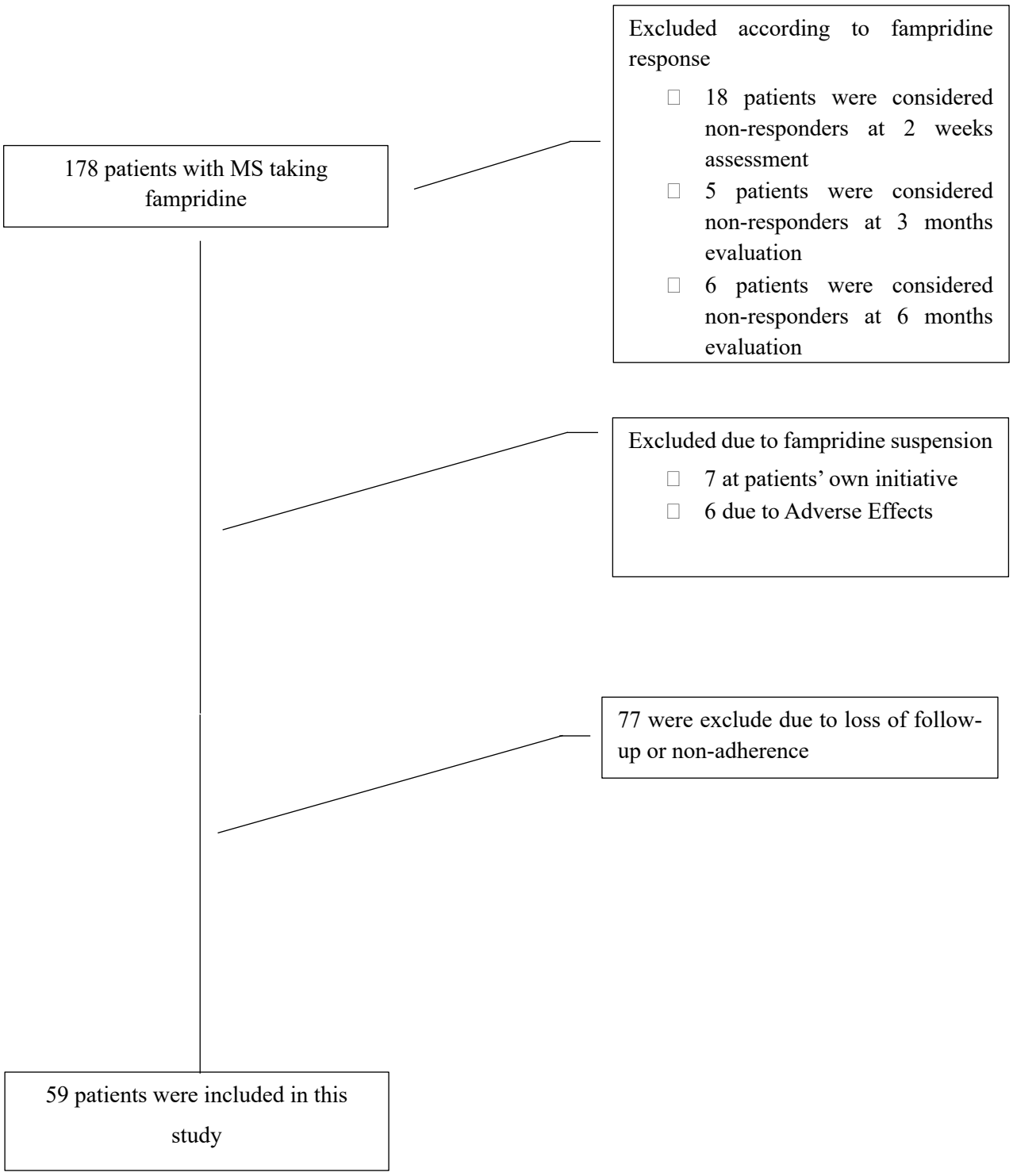


Figure 1.: Flow chart of participants and study design.

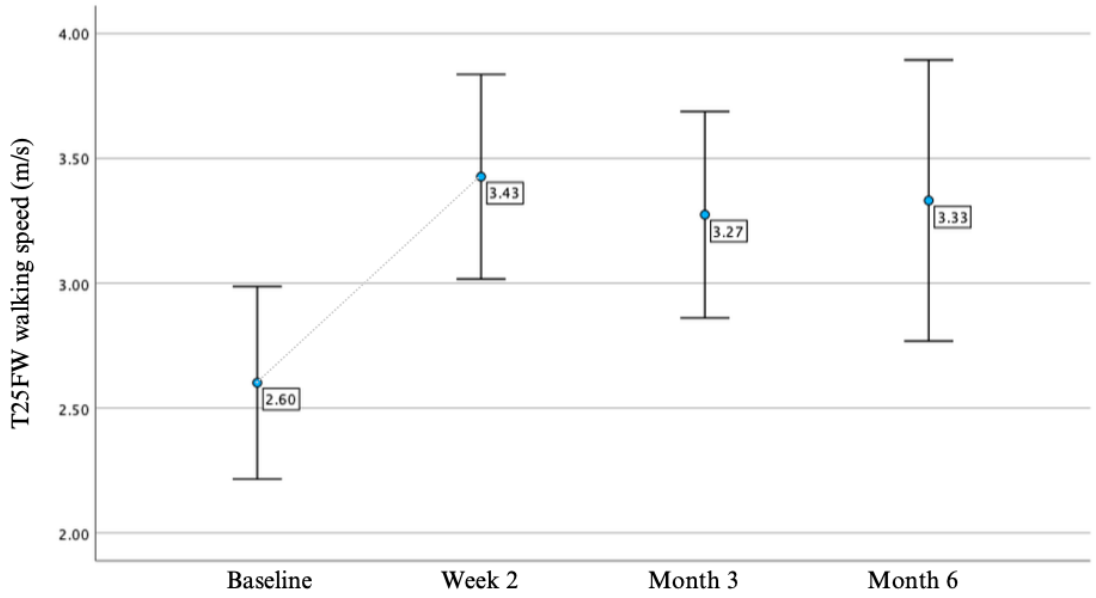


Figure 2.: Unadjusted mean score of T25FW at each time point

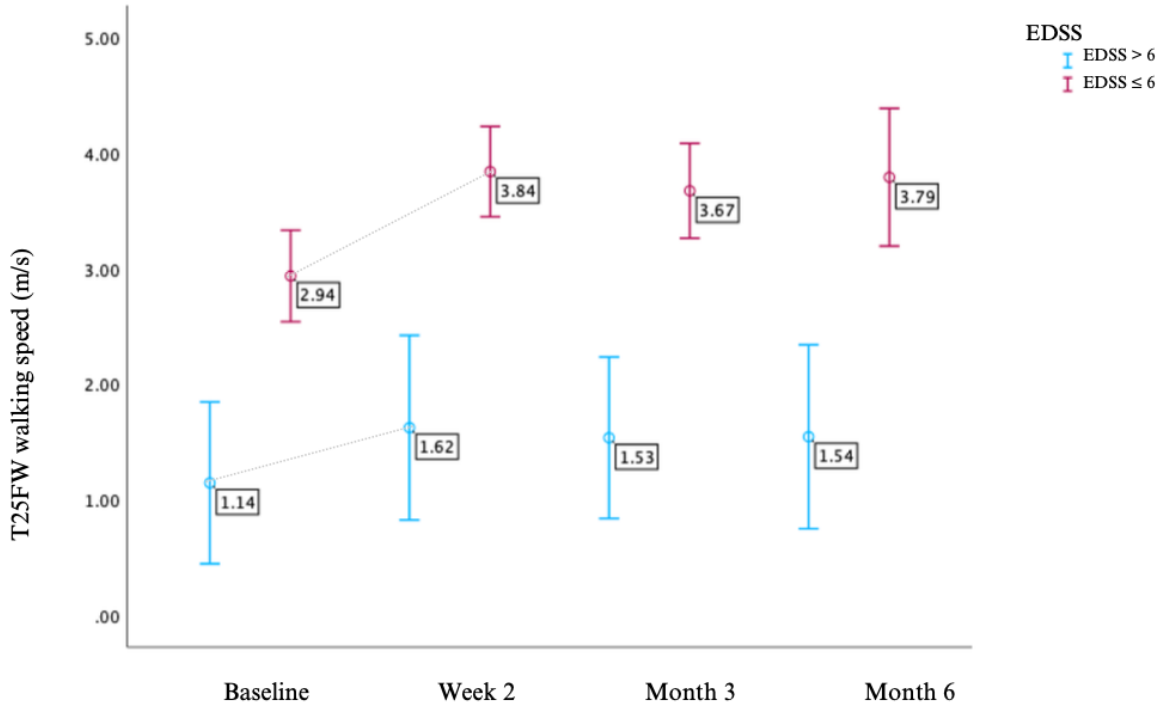


Figure 3.: Unadjusted mean score of T25FW at each time point, in patients with mild-moderate disability (EDSS ≤ 6) and severe disability (EDSS > 6)

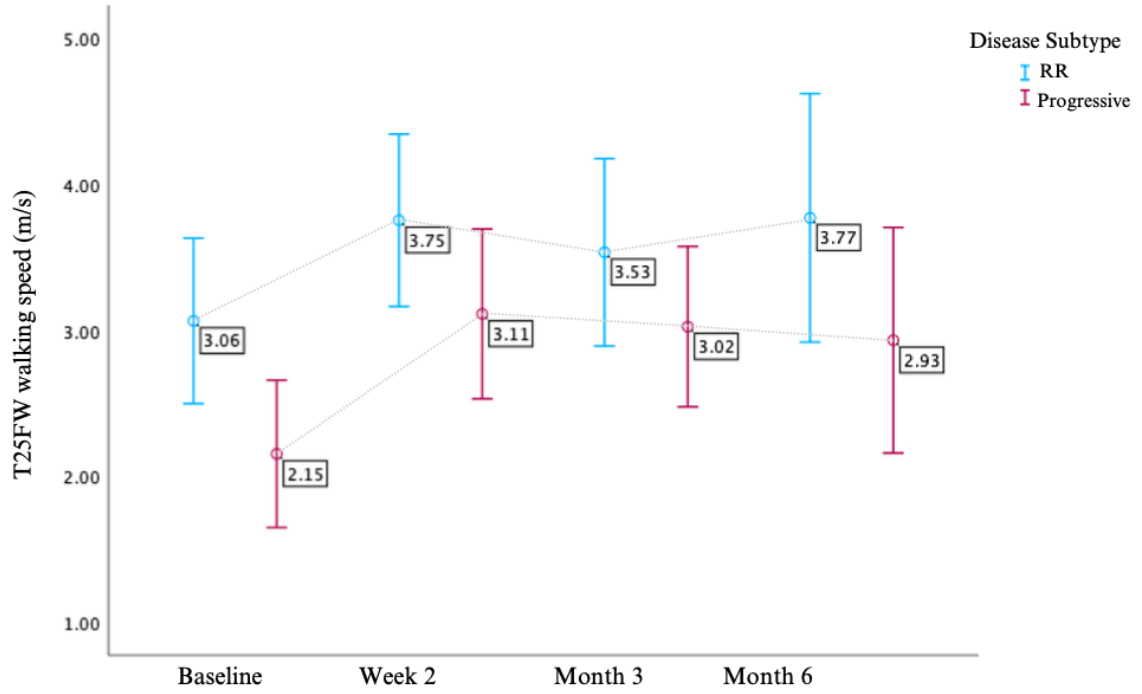


Figure 4.: Unadjusted mean score of T25FW at each time point, in patients with progressive phenotype of MS (including PP and SP) and in patients with RRMS

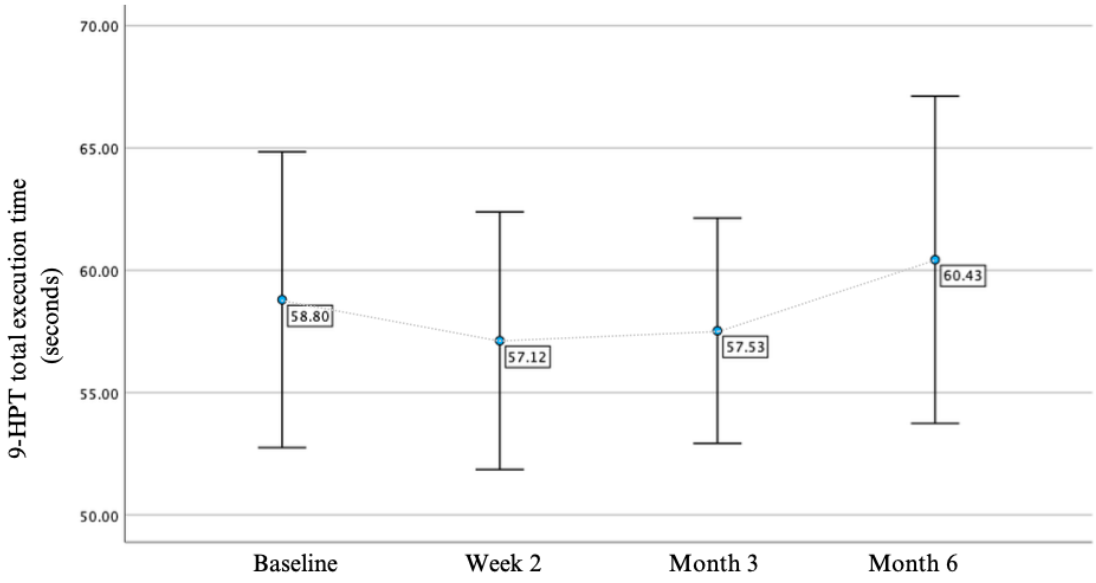


Figure 5.: Unadjusted mean score of 9HPT at each time point

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