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Sustained-release oral dalfampridine appears to have no impact on upper extremity function in people with multiple sclerosis: a randomized controlled trial

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Abstract

Background: Upper limb dysfunction is common in people with multiple sclerosis (pwMS), significantly affecting daily activities and quality of life. While dalfampridine has shown efficacy in improving gait in pwMS, its impact on upper extremity function remains unclear.

Objectives: To evaluate the effect of sustained-release oral dalfampridine on upper extremity function in pwMS.

Design: A randomized, placebo-controlled trial.

Methods: In all, 30 pwMS were randomized to receive either dalfampridine (10 mg twice daily) or a placebo for 2 weeks. Upper extremity function was assessed at baseline, after 1 week, after 2 weeks of treatment, and 2 weeks post-treatment using clinical tests (9-Hole Peg Test, Box, and Block Test, peak isometric grip force, 2-point discrimination) and self-reported questionnaires (disabilities of the arm, shoulder and hand, ability measure of the hand, Manual Ability Measurement 36). Data were analyzed using repeated-measures analysis of variance to evaluate group × time interactions.

Results: No significant group × time interactions were observed across clinical or self-reported outcomes. Both groups exhibited similar trends over time, with no measurable improvements in upper extremity dexterity, strength, or perceived function attributable to dalfampridine.

Conclusion: Sustained-release dalfampridine does not appear to improve upper extremity function in pwMS, highlighting its limitations beyond gait-related benefits. These findings underscore the need for further research to explore alternative treatments targeting upper limb dysfunction in this population.

Trial registration: ClinicalTrials.gov NCT02259361.

Plain language summary

Dalfampridine does not improve arm and hand function in people with multiple sclerosis

People with multiple sclerosis (MS) often experience difficulty using their arms and hands, which can greatly affect their daily activities and quality of life. Dalfampridine, a medication approved to help with walking in people with MS, has been studied to see if it can also improve arm and hand function. In this study, 30 people with MS were randomly assigned to take either dalfampridine (10 mg twice daily) or a placebo (a pill with no active medication) for two weeks. Researchers tested their arm and hand abilities at the start of the study, after one and two weeks of treatment, and two weeks after stopping the treatment. Tests included tasks like moving small objects, grip strength,

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and questionnaires about how participants felt about their ability to use their arms and hands. The results showed no difference between the group taking dalfampridine and the placebo group. Both groups had similar results over time, and there were no noticeable improvements in arm and hand strength, coordination, or self-reported ability linked to the medication. This study suggests that while dalfampridine may help with walking, it does not seem to improve arm and hand function in people with MS. More research is needed to find effective treatments for arm and hand challenges in this population.

Keywords: 4-aminopyridine, dalfampridine, Fampyra, hand, multiple sclerosis, upper extremity

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Introduction

Upper limb function is one of the most affected domains in people with MS (pwMS), with 50% reporting self-perceived upper limb dysfunction.[1] Dysfunction of the upper limbs in pwMS often manifests as reduced dexterity, weakness, spasticity, and sensory deficits, which collectively limit the ability to perform fine motor tasks such as buttoning clothing, writing, or eating. Although historically considered less debilitating than lower limb impairments, upper limb dysfunction is strongly associated with a loss of independence in activities of daily living, reduced quality of life, and social participation restrictions.[2,3] Despite these significant implications, therapeutic efforts and research have disproportionately focused on lower limb impairments, leaving a gap in understanding and addressing upper limb challenges in pwMS.

Various rehabilitation strategies have been implemented to improve upper limb function in pwMS, ranging from resistance and endurance training to task-oriented approaches.[4] While the evidence suggests that these interventions can enhance upper limb function, the methodological limitations, small sample sizes, and variability in study designs and outcome measures have made it challenging to draw definitive conclusions. This highlights the need for further research to explore alternative treatment approaches tailored to the specific needs of pwMS. A potential treatment alternative for upper limb deficits could be dalfampridine.

Dalfampridine, an extended-release form of 4-aminopyridine, is a potassium channel blocker. While its benefits in improving visual function and cognition, and alleviating fatigue in pwMS are controversial, its primary efficacy is firmly established in enhancing walking capacity.[5–7] By blocking potassium channels, dalfampridine increases axonal action potential propagation and improves synaptic vesicle release, enhancing synaptic and neuromuscular function. Response rates to fampridine vary widely, with many patients experiencing long-term benefits.[8] While the drug alleviates symptoms, it does not affect disease progression. Common side effects include dizziness, nervousness, and nausea, with an incidence of less than 5%.

Compared to its established use for addressing gait difficulties, cognitive impairment, and elevated fatigue, dalfampridine has been relatively underexplored as a treatment for upper limb deficits in pwMS. Marion et al.[9] investigated the effects of an 8-week dalfampridine treatment phase in 40 pwMS. Their findings indicated no significant improvements in upper limb function, as assessed by clinical tests and electrophysiological measures. Similarly, Korsen et al.[10] reported no pre-post differences in 9-Hole Peg Test scores following dalfampridine treatment. By contrast, two previous studies reported a positive impact of dalfampridine on hand function in pwMS.[11,12] A major limitation in this field of research is the frequent lack of placebo-controlled designs, resulting in participants not being blinded to their treatment allocation. In addition, upper limb function is often evaluated as a secondary outcome rather than a primary focus. This study aims to address these gaps by employing a randomized controlled trial (RCT) with a placebo-controlled design to rigorously evaluate the effects

of oral dalfampridine on upper limb function assessed via subjective and objective measurement tools in pwMS.

Methods

Study design and participants

The implemented study design was executed according to the rigor of the CONSORT guidelines.[13] The RCT was a single-center, double-blinded, placebo-controlled design performed at the Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, Israel. Eligible PwMS were enrolled according to the following criteria: (1) diagnosis of clinically definite relapsing-remitting MS according to the revised McDonald criteria 2017,[14] (2) 18–70 years of age, and (3) scored between 50 and 90 on the upper limb Motricity Index test, at the time of informed consent. This test evaluates strength during three essential movements (pinch grasp, elbow flexion, and shoulder abduction).[15] The selected score range criteria determine patients who suffer a moderate decline in function abilities of the upper limb. Exclusion criteria were as follows: (1) MS clinical relapse or treatment with corticosteroid therapy within 3 months before enrollment, (2) patients experiencing major depression or cognitive decline limiting understanding simple instructions, (3) orthopedic disorders that could negatively affect upper limb movement, and (4) changes in the immunomodulatory medications during the study. All participants gave informed consent before participation. Approval was obtained from the Sheba Medical Center Independent Ethics Committee before the commencement of the study (# SMC-038013).

Study protocol

In all, 30 participants were recruited through referrals from neurologists at the MS center and advertisements inviting potential patients to participate. Resource constraints determined the sample size. However, we considered that the data collected in this study will contribute to enhancing the findings and conclusions of future meta-analyses on this topic. Participants were randomly assigned to receive either 10 mg dalfampridine or a placebo, taken twice daily for 2 weeks. The medication and placebo were prepared as identical tablets and packaged in indistinguishable bottles (kits), each labeled with a unique code generated through a pre-determined randomization sequence. After providing informed consent, participants were assigned a random kit by the study coordinator, who remained blinded to the allocation. Outcome measures were assessed at four time points: (1) baseline (prior to starting the intervention), (2) after 1 week of treatment, (3) at the end of the 2-week treatment period, and (4) during a follow-up visit 2 weeks after the final dose. Assessments were conducted by an independent assessor (occupational therapist) who was also blinded to the treatment allocation. The allocation codes were securely stored and unblinded only at the end of the trial after all data collection and entry had been completed. This rigorous methodology minimized bias and maintained the integrity of the study, providing reliable data on the effects of dalfampridine on upper extremity and dexterity functions.

Outcome measures

9-HPT—primary outcome measure. The 9-HPT is a brief, standardized, quantitative finger dexterity test.[16] Both the dominant and non-dominant hands were tested twice. Participants were seated at a table, where a small, shallow container holding nine pegs and a plastic block containing nine empty holes was placed. Upon receiving the start command, a stopwatch was activated, and participants proceeded to pick up the nine pegs, one at a time, as quickly as possible, placing them into the nine holes. Once all pegs were in the holes, participants removed them as quickly as possible, one at a time, returning them to the shallow container. The total time to complete the task was recorded for each trial. Two consecutive trials with the dominant hand were immediately followed by two consecutive trials with the non-dominant hand. The score for the dominant hand was calculated as the average time of the two trials performed with that hand, and the score for the non-dominant hand was calculated similarly. The 9-HPT has high inter-rater reliability, good test–retest reliability, concurrent and convergent validity, and sensitivity to detect minor hand function impairments in pwMS.[17]

Box and Block Test. The Box and Block Test (BBT) assessed gross manual dexterity.[18] The test apparatus consisted of a wooden box divided into two compartments by a 15.2 cm high partition and 150 wooden blocks, each measuring 2.5 cm.

Participants were instructed to transfer as many blocks as possible, one at a time, from one compartment to the other within 60 s. A 15-s trial period was provided for each hand before the timed test began. The number of blocks successfully transferred to the opposite compartment was recorded, with higher scores indicating better manual dexterity. Testing started with the dominant hand and was repeated with the non-dominant hand. The BBT has well-established psychometric properties in neurological populations.[19]

Peak isometric grip force. Peak isometric grip force was measured using the Jamar hand-held dynamometer (Biometrics Ltd, Ladysmith, VA, USA), a device designed to assess grip strength in functional evaluations. Participants were seated with their shoulder adducted and neutrally rotated, elbow flexed at 90°, and forearm in a neutral position. The wrist was positioned between 0° and 30° dorsiflexion and 0° and 15° ulnar deviation. The dynamometer was held freely, without support, and adjusted so that the proximal interphalangeal joints aligned with the handle. Participants were instructed to exert maximal force, and the peak value of two trials was recorded for each hand, starting with the dominant side.

Two-point discrimination. The two-point discrimination (2PD) test assessed tactile perception.[20] Testing was conducted on the anterior aspect of the finger pads using a modified 4-2-1 stepping algorithm. Participants were seated in a quiet room, blindfolded, and tested starting with a 5 mm distance gap. The gap was adjusted in increments of 3, 2, or 1 mm based on the participant's responses until the smallest gap reliably recognized (>50% of trials) was determined. Random null trials were interspersed to ensure response accuracy, and the test was paused if participants incorrectly responded to both null trials. The final score was the average threshold across all tested digits.

Disabilities of the arm, shoulder, and hand. The disabilities of the arm, shoulder, and hand (DASH) is a 30-item questionnaire designed to measure physical function and symptoms in individuals with upper limb disorders.[21] Each item is scored on a scale from 1 (no difficulty) to 5 (unable), and a total score is calculated by averaging the item scores to produce a mean value between 1 and 5. This mean score is then transformed to a scale of 0–100 using the formula: $((\text{mean score} - 1) \times 25)$. Higher scores indicate greater disability. The DASH is a reliable and valid tool for assessing upper limb function in pwMS.[22]

ABILHAND assessment. The ability measure of the hand (ABILHAND) is a patient-reported outcome measure designed to assess manual ability in individuals with upper limb impairments.[23] It consists of 23 items evaluating the ease or difficulty of performing bimanual daily activities, such as opening a jar or buttoning a shirt. Participants rate their perceived ability for each task on a 3-point scale: 0 (impossible), 1 (difficult), and 2 (easy). The total score is calculated by summing the item responses and converting them to a linear scale using Rasch analysis. Higher scores indicate greater manual ability. The ABILHAND has been validated as a reliable tool for assessing upper limb function in populations with neurological disorders, pwMS.[24]

Manual Ability Measurement 36. The Manual Ability Measurement 36 (MAM-36) is a self-reported questionnaire designed to evaluate manual ability in individuals with upper limb impairments.[25] It includes 36 items that assess the participant's perceived ease or difficulty in performing various daily activities, such as writing, eating, or using household tools. Each item is rated on a 4-point scale: 1 (cannot do it at all), 2 (can do it with difficulty or partially), 3 (can do it easily with an adapted method), and 4 (can do it easily without difficulty). A total score is calculated by summing the item responses and normalizing the score to a 0–100 scale, with higher scores reflecting better manual ability. The MAM-36 has been validated in various clinical populations, including pwMS,[26] and is recognized for its reliability, sensitivity, and responsiveness in assessing changes in manual function.

Statistical analysis

Data were analyzed using a repeated-measures analysis of variance to evaluate the effects of the intervention (dalfampridine vs placebo) over time. The primary outcomes included changes in upper extremity and dexterity functions at the four time points: baseline, after 1 week, after 2 weeks, and at the 2-week follow-up. The model included group (dalfampridine vs placebo) as the between-subjects factor, time as the within-subjects factor, and group × time interaction to assess

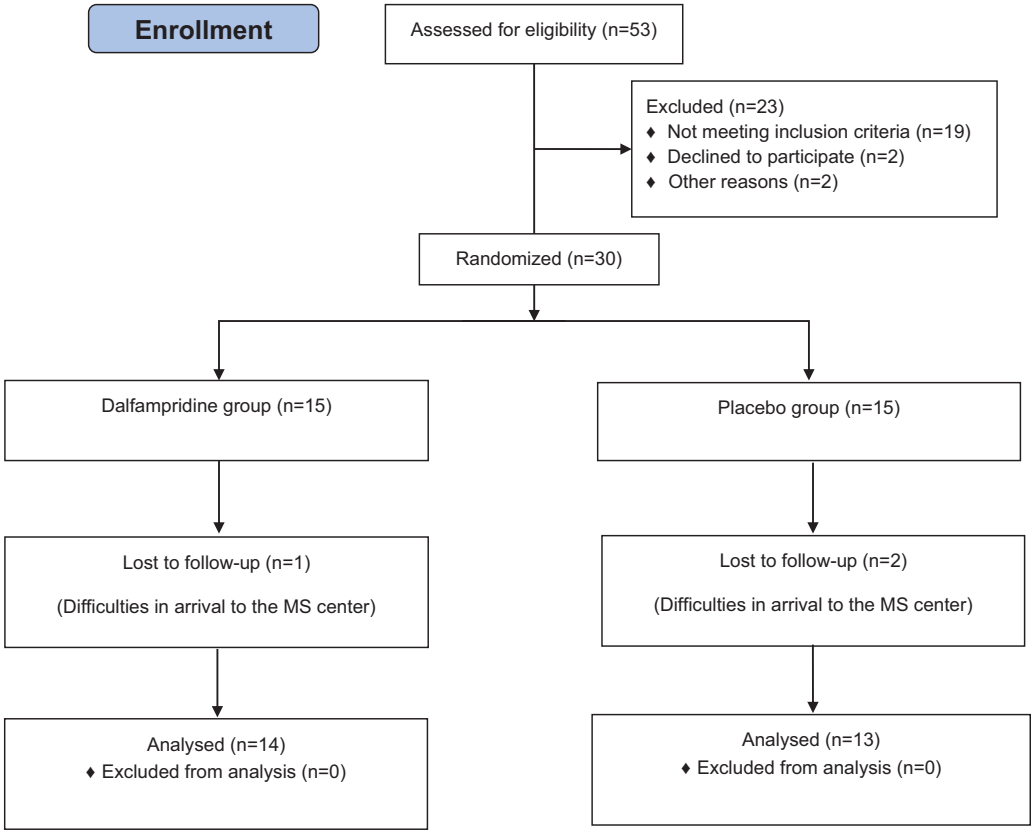

Figure 1. Flow chart of the study.

differential changes between groups over time. Post hoc pairwise comparisons with Bonferroni corrections were conducted to identify significant differences between specific time points within and between groups. Continuous variables were assessed for normality using the Shapiro–Wilk test, and non-parametric alternatives were employed for variables that violated normality assumptions. Missing data were handled using multiple imputations based on the expectation-maximization algorithm. All analyses were conducted using the SPSS software, with a significance level set at $p < 0.05$.

Results

The study initially included 30 participants divided equally between groups. However, three participants dropped out, one from the medication group and two from the placebo group. Consequently, 27 participants completed the trial, with 14 in the medication group and 13 in the placebo group (Figure 1). Baseline comparisons showed no significant differences between the groups for demographic or clinical characteristics, including age, gender distribution, type of MS, dominant hand, disease duration, and expanded disability status scale scores ($p > 0.05$), confirming that the two groups were well-matched at baseline (Table 1). Adverse effects were reported by two participants from the medication group (one experienced dizziness and one headache) and one participant from the placebo group (nausea).

Across all outcome measures (Table 2), no significant group × time interactions were observed, indicating that dalfampridine had no measurable impact on upper extremity and dexterity functions compared to placebo. For the 9HPT, BBT, and peak isometric grip force, both groups demonstrated similar performance trends over time, with no meaningful changes in scores for either the dominant or non-dominant hand ($p > 0.05$). A significant main effect of time was observed for 2PD in the dominant hand ($p = 0.028$), suggesting overall improvement, but this change was not associated with the intervention (group × time interaction, $p = 0.149$).

Table 1. Demographics and clinical characteristics of the study groups.

Variable	Mean (SD)		*p*-Value
	Medication ($n = 14$)	Placebo ($n = 13$)	
Age (years)	45.8 (10.0)	51.0 (7.6)	0.161
Gender (M/F)	6/8	6/7	0.500
Type of MS (RR/P)	10/4	10/3	0.865
Dominant hand (R/L)	11/3	9/4	0.432
Disease duration (years)	15.8 (8.2)	20.4 (13.0)	0.352
EDSS	6.5 (2.0–8.0)	6.0 (2.0–8.0)	0.194
Pyramidal	4.0 (2.0–5.0)	3.5 (0–5.0)	0.168
Cerebellar	2.0 (0–3.0)	2.0 (0–3.0)	1.000
Sensory	1.0 (0–3.0)	1.5 (0–4.0)	1.000
Brain stem	1.0 (0–3.0)	1.0 (0–3.0)	0.486
Visual	0 (0–3.0)	0 (0–2.0)	0.168
Bowel and bladder	0 (0–4.0)	0 (0–5.0)	0.895
Cerebral	0 (0–3.0)	0 (0–3.0)	0.884

EDSS, expanded disability status scale.

Self-reported questionnaire scores, including DASH, ABILHAND, and MAM-36, also showed no significant differences between groups over time ($p > 0.05$). Overall, the findings indicate no treatment effect of dalfampridine on the assessed outcomes throughout the treatment phase.

Discussion

Using a randomized, placebo-controlled trial, this study evaluated the impact of sustained-release dalfampridine on upper extremity function in pwMS. The findings demonstrated that dalfampridine did not yield significant improvements in upper extremity function compared to the placebo group. Across all clinical tests, including the 9HPT, BBT, and peak isometric grip force, no meaningful group × time interactions were observed. Similarly, self-reported questionnaire scores (DASH, ABILHAND, and MAM-36) indicated no significant differences between groups over time. These results collectively suggest that a 2-week treatment phase of dalfampridine has no measurable impact on upper extremity dexterity, strength, or perceived function in pwMS.

The current findings align with several previous studies,[9,10,27,28] while conflicting with others.[11,12] Notably, to the best of our knowledge, among studies investigating this subject, only Marion et al.[9] assessed upper limb function using tools beyond the 9HPT. In most previous studies,[10–12,27,28] the 9HPT was the sole assessment for upper limb function and was typically treated as a secondary or tertiary outcome measure. A key strength of our study is the comprehensive evaluation of upper limb function, incorporating grip strength, gross and fine manual dexterity, tactile perception, and subjective assessments via multiple patient-reported outcome measures. Furthermore, this study is one of the few to include a placebo-controlled group.[9,27,28] Consistent with these placebo-controlled studies, we also found that dalfampridine had no measurable effect on upper limb function. Collectively, these findings reinforce the conclusion that dalfampridine does not improve upper limb function in pwMS.

Table 2. Outcome measures according to study time points and group allocation.

Parameter	Medication ($n = 14$)				Placebo ($n = 13$)				F (p-value) for time	F (p-value) for group × time
	Baseline	1-Week	2-Week	2 Weeks follow-up	Baseline	1-Week	2-Week	2 Weeks follow-up		
9HPT (s)										
Dominant	71.8 (75.6)	42.0 (17.4)	68.3 (88.7)	75.5 (79.8)	63.0 (76.6)	63.2 (82.4)	66.5 (89.0)	65.5 (89.2)	0.973 (0.433)	1.163 (0.359)
Non-dominant	64.0 (52.5)	50.1 (28.7)	53.1 (32.6)	59.7 (39.9)	59.0 (59.8)	47.9 (33.4)	43.7 (23.2)	43.3 (22.8)	1.867 (0.176)	1.023 (0.409)
BBT (s)										
Dominant	28.8 (19.7)	30.3 (19.3)	31.0 (20.5)	29.9 (21.2)	25.4 (11.1)	28.0 (13.3)	27.1 (13.3)	27.5 (13.7)	1.529 (0.239)	0.479 (0.701)
Non-dominant	33.4 (12.3)	36.1 (16.3)	36.4 (15.3)	35.7 (18.1)	26.2 (13.4)	30.8 (13.3)	31.0 (15.0)	30.9 (14.6)	2.872 (0.069)	0.233 (0.872)
Peak isometric grip force (kg)										
Dominant	16.8 (13.5)	15.6 (11.5)	15.6 (12.6)	14.7 (9.7)	21.1 (11.6)	21.3 (12.1)	22.3 (10.8)	21.0 (13.1)	0.591 (0.629)	0.488 (0.695)
Non-dominant	18.6 (8.3)	18.5 (8.4)	19.1 (9.8)	18.5 (9.5)	19.7 (15.9)	21.4 (15.8)	21.9 (15.1)	21.6 (16.5)	1.102 (0.374)	0.725 (0.550)
2PD (mm)										
Dominant	8.1 (3.1)	6.8 (3.2)	6.4 (2.6)	5.8 (2.2)	5.9 (3.2)	5.9 (2.5)	5.6 (2.7)	5.6 (2.7)	3.839 (0.028)	2.008 (0.149)
Non-dominant	6.8 (3.0)	6.4 (2.3)	6.3 (2.3)	6.3 (0.8)	5.8 (3.9)	5.8 (3.9)	5.9 (4.0)	5.9 (4.1)	0.130 (0.941)	0.420 (0.741)
Self-reported questionnaire (score)										
DASH	62.7 (22.2)	–	60.1 (17.8)	62.9 (23.0)	57.1 (23.7)	–	51.6 (26.7)	50.3 (29.1)	1.538 (0.245)	0.934 (0.413)
ABILHAND	22.9 (9.1)	–	25.1 (8.1)	24.3 (9.3)	28.9 (15.5)	–	29.5 (15.9)	30.1 (16.1)	0.857 (0.443)	0.780 (0.475)
MAM-36	95.4 (25.6)	–	97.9 (15.5)	94.5 (29.5)	101.5 (33.4)	–	105.3 (36.8)	103.9 (33.4)	0.501 (0.615)	0.020 (0.848)

2PD, two-point discrimination; 9HPT, nine-Hole Peg Test; ABILHAND, ability measure of the hand; BBT, Box and Block Test; DASH, disabilities of the arm, shoulder and hand; MAM-36, Manual Ability Measurement 36.

A possible explanation for the lack of significant findings in the current study is that dalfampridine's primary mechanism of action, improving action potential conduction in demyelinated nerves, may be more effective for gross motor functions, such as walking, than for fine motor skills, which rely on complex neuromuscular coordination. In addition, the clinical outcome measures used in this study may lack the sensitivity needed to detect subtle changes in upper limb function. It is plausible that using advanced instrumented devices, such as wearable sensors or video-based motion analysis, could provide a more precise assessment of upper limb dexterity and reveal effects that conventional methods might miss. Future research should consider incorporating laboratory-based measurement tools to better elucidate dalfampridine's potential impact on upper limb function.

A strength of the study, compared with previous studies on this topic, was the use of both clinical upper limb tests and patient-reported outcome measures, which were collected at baseline, at the end of the treatment phase, and at the 2-week follow-up. Nevertheless, several limitations should be acknowledged. First, the relatively small sample size may have limited the statistical power to detect subtle effects of dalfampridine on upper limb function, reducing the generalizability of the findings. Second, the treatment period was 2 weeks, which aligns with some studies but is shorter than others lasting up to 14 or 18 weeks. However, we believe that if dalfampridine is effective, its impact should emerge rapidly, as has been consistently demonstrated in studies on its effects on gait.[29] Third, while the study employed a comprehensive set of outcome measures, it relied primarily on clinical assessments and self-reported questionnaires, which may lack the sensitivity to detect nuanced changes in upper limb function. Incorporating advanced tools, such as wearable sensors, video-based motion analysis, or electrophysiological measurements, could enhance precision and provide deeper insights into the drug's effects. Addressing these limitations in future research will help clarify dalfampridine's role in upper limb rehabilitation for pwMS.

Future research should examine whether extended treatment durations or alternative dosing regimens of dalfampridine could improve upper limb function. Larger, multicenter trials with advanced assessment tools, such as kinematic analysis, wearable sensors, and electrophysiological measurements, are needed to detect subtle changes and clarify the drug's effects. Identifying specific subgroups of pwMS who may benefit from dalfampridine, based on disease phenotype or impairment severity, could further refine its therapeutic applications. Finally, combining dalfampridine with targeted rehabilitation interventions may also uncover potential synergistic benefits for upper limb function.

Conclusion

This study demonstrates that dalfampridine does not enhance upper limb function in pwMS, underscoring its limitations beyond improving gait. Clinicians should prescribe dalfampridine with a clear focus on its proven efficacy for mobility impairments and avoid extending its use to upper limb dysfunction without supporting evidence. These findings help manage patient expectations and ensure treatment goals are grounded in evidence-based outcomes, refining the therapeutic role of dalfampridine in clinical practice.

Declarations

Ethics approval and consent to participate

The study was approved by the Sheba Institutional Review Board (Ref# SMC-0380-13), consistent with the Declaration of Helsinki. All subjects signed an informed consent form before participation.

Consent for publication

Not applicable.

Author contributions

Shay Menascu: Conceptualization; Investigation; Resources; Writing – review & editing.

Lior Frid: Investigation; Project administration; Writing – review & editing.

Alon Kalron: Conceptualization; Formal analysis; Methodology; Supervision; Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data supporting this study's findings are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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