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Review Article

Effect of Fampridine on cognition in patients with multiple sclerosis (MS): a systematic review and meta-analysis

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Abstract

Background: Cognitive impairment (CI) is a disabling complication in patients with multiple sclerosis (MS). Fampridine is used to improve walking abilities in subjects with MS while it is also used for improving cognition, although the results are heterogeneous. Therefore, we aimed to conduct a systematic review and meta-analysis to investigate the effect of fampridine on cognition in patients with MS.

Methods: We performed a comprehensive search in PubMed, EMBASE, Scopus, Web of Science, google scholar, and also gray including references of the references and conference abstracts on January 1th 2020. We extracted data regarding the number of participants, first author, publication year, and country of origin, age, disease duration, Expanded Disability Status Scale (EDSS), duration of follow up, type of cognition test, and scores before and after the treatment.

Results: We identified 4972 studies in the preliminary search. After deduplication, 2607 articles remained. Two researchers screened the title and the abstracts, removing 2590 studies. Finally, 15 studies remained for meta-analysis. The included studies were published between 2013 and 2021, and the most frequent country of origin was Denmark. The mean age of participants of the studies ranged between 39 and 53 years and the mean EDSS ranged between 4 and 5.8, respectively. The SMD (standardized mean difference) of Symbol Digit Modalities Test (SDMT) (after-before treatment) was 0.45(95%CI: 0.06-0.84) (I^2=75.3%, p<0.001). The SMD of Paced Auditory Serial Addition Test (PASAT) (after-before treatment) was 0.25 (95%CI: 0.13-0.37) (I^2=84.3%, p<0.001)

Conclusions: Fampridine has a significant role in decreasing cognitive impairments is MS patients.

Keywords: Multiple sclerosis, Cognition, Fampridine.

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) with unknown etiology. MS causes demyelination of CNS neurons and signaling impairments which generate a variety of signs and symptoms. Patients with MS suffer from psychological and physical disabilities including walking disability, depression, fatigue, and cognitive impairment which impair their quality of life (1-6). CI is prevalent in patients with MS which interferes with daily activities, occupation, social activities, and quality of life (7). It is reported that between 40-65% of affected cases suffer from CI which is present from the early stages of the disease (8). All aspects of cognition especially information processing speed and memory (9). To improve cognition in subjects with MS different medications such as memantine, rivastigmine and donepezil are administered while their safety and efficacy are not satisfactory (10-12). Fampridine which is also called 4-aminopyridine is a fat-soluble medication that crosses the blood-brain barrier easily (13).

Fampridine enhances action-potential conduction in demyelinated nerve fibers and facilitates synaptic transmission (13). It improves muscle strength and walking speed in patients with MS and routinely is used for walking difficulties in MS (6). Based on its effects on demyelinated axonal fibers in different sites of the CNS, it is suggested to positively improve psychological well-being like depression and fatigue in MS (6, 14). Up to now, different studies showed the effects of fampridine on cognition based on various tests. Some of them show significant improvement after treatment and others did not confirm the efficacy profile. Therefore, we aimed to conduct a systematic review and meta-analysis to investigate the effect of fampridine on cognition in patients with MS.

Methods

We performed a comprehensive search in PubMed, EMBASE, Scopus, Web of Science, google scholar, and also gray including references of the references and conference abstracts on January 1th 2020. After deleting duplicate articles, two independent researchers screened the titles and abstracts of the potentially eligible studies. In the case of discrepancy, they asked the third one. Afterward, they screened the full texts of the remained studies and extracted the data.

The extracted data were entered by each researcher in a separate datasheet. Another expert researcher checked the two data sheets to solve the discrepancies. Data extraction was performed based on a predefined table including: number of participants, first author, publication year, country of origin, age, disease duration, Expanded Disability Status Scale (EDSS), duration of low up, type of cognition test, and scores before and after the treatment.

The MeSH terms were: ((Multiple Sclerosis) OR (Sclerosis AND multiple) OR (sclerosis AND disseminated) OR (disseminated sclerosis) OR ((multiple sclerosis) AND (acute fulminating)) AND ((4 Aminopyridine) OR Dalfampridine OR Pymadine OR VMI-103 OR (VMI 103) OR VMI103 OR (4-Aminopyridine Sustained Release) OR (4 Aminopyridine Sustained Release) OR ((Sustained Release) AND 4-Aminopyridine) OR Fampridine-SR OR (Fampridine SR) OR Fampridine)

Inclusion criteria were defined as follows: Before-after studies trials reporting scores of the tests before and after treatment, articles published in English.

Exclusion criteria were defined as follows: 1) Case-control, Letters to the editor, Cross-sectional, and Case report studies 2) Studies that had no clear data regarding the scores of the cognition tests.

Risk of bias assessment: Two independent researchers performed risk of bias assessment using the Cochrane Collaboration's tool for assessing the risk of bias and Newcastle - Ottawa Quality Assessment Scale (adapted version for cohort studies) (15, 16).

Statistical analysis: For this study, we performed all statistical analyses using STATA 14.0 (Stata Corp LP, College Station, TX, USA). Standardized mean difference (SMD) was calculated and presented as the effect size for all outcomes. To determine heterogeneity, Inconsistency (I^2) of included studies was calculated. We used random-effects model for meta-analysis as the heterogeneity between study results (I^2) was more than 50%.

Results

We identified 4972 studies in the preliminary search. After deduplication, 2607 articles remained. Two researchers screened the title and the abstracts, removing 2592 studies. Finally, 15 studies remained for meta-analysis (figure 1). The included studies were published between 2013 and 2021 and were conducted in 10 countries including Denmark, Germany, Greece, Italy, Mexico, Switzerland, USA, Canada, Spain, and Slovenia. Totally, 723 patients were included in meta-analysis with the mean age in range of 39 and 53 years. Also, in the included studies patients had the mean EDSS ranged between 4 and 5.8 (table 1). The SMD of SDMT (after-before treatment) was 0.45(95%CI: 0.06-0.84) (I^2=75.3%, p<0.001) (figure 2). The SMD of PASAT (after-before treatment) was 0.25(95%CI: 0.13-0.37) (I2=84.3%, p<0.001) (figure 3). The risk of bias assessment of included studies is summarized in table 2.

Discussion

To our knowledge, this is the first systematic review and meta-analysis which focused only on the effects of fampridine on cognition status in patients with MS. Our results demonstrated that fampridine treatment significantly improved scores of both SDMT and PASAT, indicating positive effects of treatment on cognition in patients with MS. In a previous systematic review and meta-analysis which aimed to assess the effects of fampridine on walking, cognition, and quality of life, Valet et al. included only four studies for the cognition part and reported no significant improvement after treatment, although its effects on walking were significant (30).

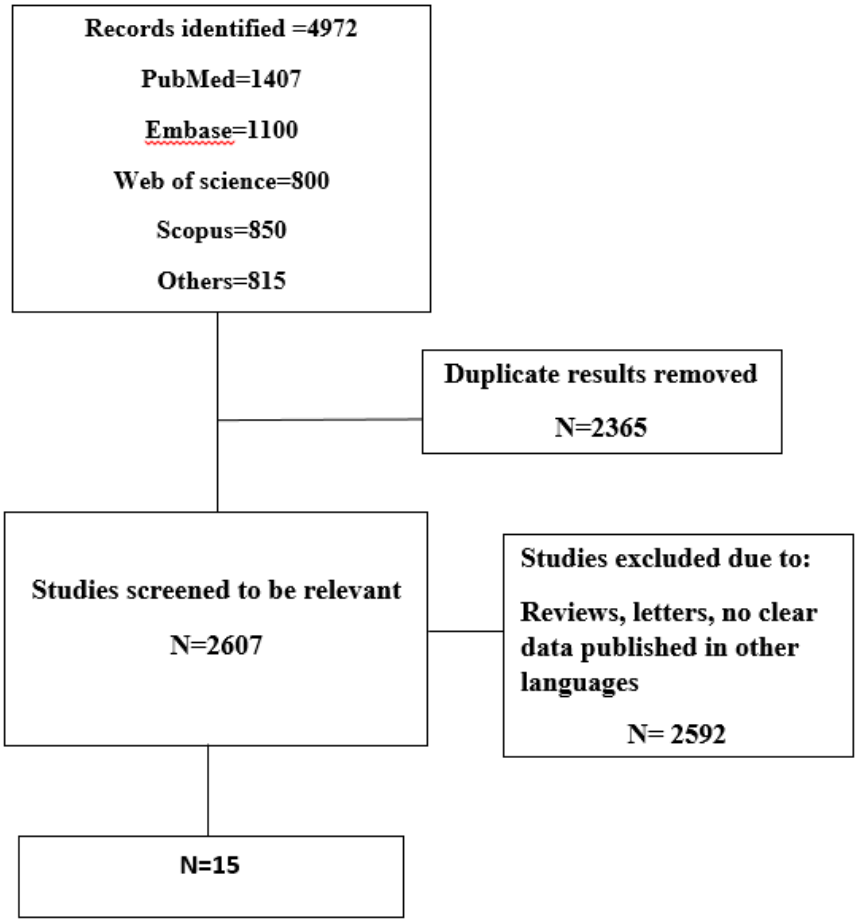

Figure 1. Flow diagram of included studies

Table 1. Data extracted from included studies.

Author	Year	Country	Number Female Male	Age	Disease duration Mean (SD) year	EDSS Mean (SD)	Follow up	Drug type	Cognition test	Pretreatment in Fampridine group	Post treatment in Fampridine group	Quality assessment
Sepehr Mamoei (17)	2021	Denmark	39	NR	NR	NR	12 W	Fampridine	SDMT	40.2 (10.6)	38.7 (9.8)	
Dimos D. Mitsikostas (6)	2021	Greece	94	NR	NR	NR	24 W	PR-FAM	PASAT	30.64 (21.358)	31.72 (21.874)	6 /9
Francisco Alejandro Rodriguez-Leal (18)	2019	Germany	189	53.55 (10.83)	12.92 (10.83)	5.22 (1.29)	2 W	Fampridine	PASAT	45.15 (12.17)	46.62 (11.91)	7 /9

Author	Year	Country	Number Female Male	Age	Disease duration Mean (SD) year	EDSS Mean (SD)	Follow up	Drug type	Cognition test	Pretreatment in Fampridine group	Post treatment in Fampridine group	Quality assessment
Laura De Giglio (19)	2019	Italy	80 50 30	49.3 (78)	14.7 (9)	Median (range) 4(1-6)	4 W	ER-FAM	PASAT	28.5 (12.6)	Mean (SD) in 70 patients 35.9 (11.70)	
Laura De Giglio (19)	2019	Italy	80 50 30	49.3 (78)	14.7 (9)	Median (range) 4 (1-6)	4 W	ER-FAM	SDMT	30.1 (7.2)	Mean (SD) in 70 patients 39.8 (9.196)	
C. Arreola-Mora (20)	2018	Mexico	11 7 4	39.5 (8)	8.55 (5.9)	4.7 (1.4)	21-22 W	Fampridine	SDMT	37.9 (11.1)	41.3 (13.9)	
C. Arreola-Mora (20)	2018	Mexico	11 7 4	39.5 (8)	8.55 (5.9)	4.7 (1.4)	21-22 W	Fampridine	PASAT	33.7 (11.4)	35 (14.3)	
C. Bakirtzis (21)	2018	Greece	35 17 18	Mean (median) 52.4 (52)	Mean (median) 14.4 (14)	Mean 5.3	24 W	PR-FAM	SDMT	32 (13.6)	35.6 (14.6)	5 /9
Sarah D. Broicher (14)	2018	Switzerland	20	NR	NR	NR	22 M	Fampridine	SDMT	47 (3.1)	50.5 (4.7)	
Elizabeth W. Triche (22)	2016	USA	31 24 7	53.7 (10.3)	13.1 (8.8)	5.1 (1.7)	14 W	ER-FAM	SDMT	median (25th, 75th): 40.0 (29.0, 45.0)	41.0 (35.0, 48.0)	5 /9
H.B Jensen (23)	2016	Denmark	16 7 9	50.8 (6.5)	9.5 (5.4)	5.8 (0.8)	26-28 D	SR-FAM	SDMT	39 (10)	41.3 (13.1)	
Sarah A. Morrow (24)	2016	Canada	24	NR	NR	NR	4 W	SR-FAM	PASAT	44.9 (11)	46.7 (10.3)	
Melanie Korsen (25)	2015	Germany	22 15 7	48.0 (10.4)	NR	4.0 (4.0–5.0)	12-14 D	ER-FAM	PASAT	42.9 (13.5)	46.1 (13.3)	4 /9

Author	Year	Country	Number Female Male	Age	Disease duration Mean (SD) year	EDSS Mean (SD)	Follow up	Drug type	Cognition test	Pretreatment in Fampridine group	Post treatment in Fampridine group	Quality assessment
I. González-Suárez (26)	2015	Spain	10 7 3	53.78 (8.012)	NR	5.72 (0.67)	6 M	Fampridine	SDMT	34.71 (7.41)	40.57 (9.81)	NA
Katja Pavsic (27)	2015	Slovenia	17	NR	NR	NR	28 D	Fampridine	PASAT	42.1 (10.1)	43.4 (10.8)	4 / 9
HB Jensen (28)	2014	Denmark	105	48.6 (7.1)	10.8 (7.2)	5.6 (0.9)	4 W	SR-FAM	SDMT	37. 4(13.2)	38.7 (13.6)	
T. Ruck (29)	2013	Germany	30	NR	NR	NR	9-12 M	ER-FAM	PASAT	39.45 (2.84)	46.35 (2.84)	5/9

PASAT=Paced Auditory Serial Addition Test, SDMT=Symbol Digit Modalities Test, ER-FAM=extended release of Fampridine, PR-FAM=prolonged release of Fampridine, SR-FAM=slow release of Fampridine, NR=not reported, NA=not applicable, ABS*=abstract, QA=quality assessment, D= day, M=month, W= week, SD=standard deviation, SE=standard error, CI= confidence interval.

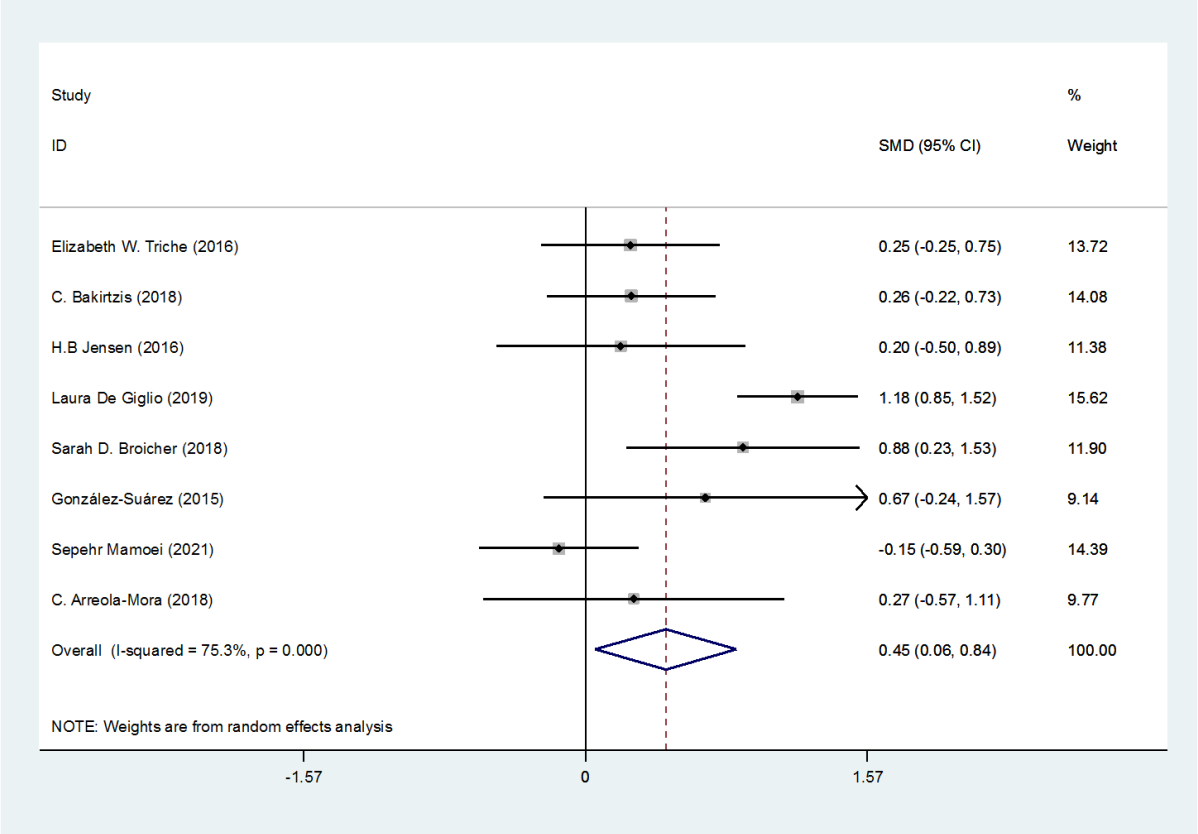

Figure 2. The SMD of SDMT (after-before treatment)

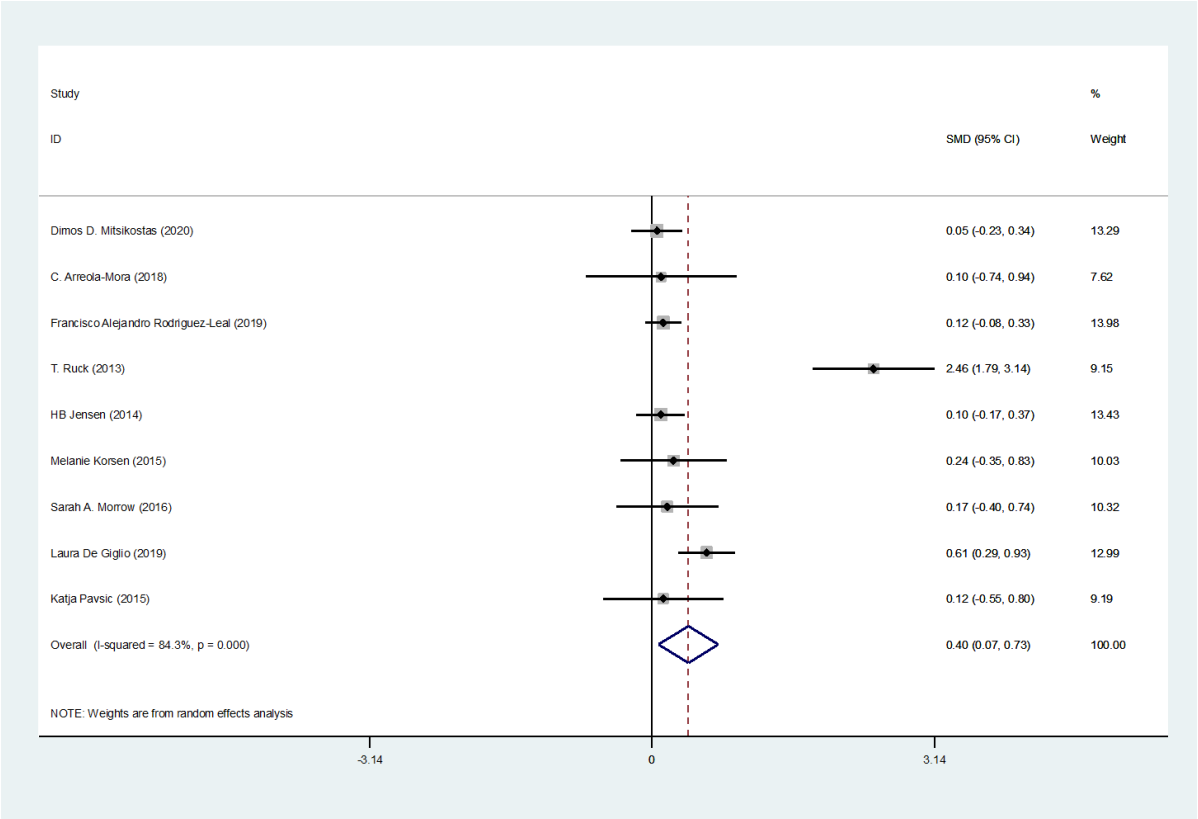

Figure 3. The SMD of PASAT (after-before treatment).

Table 2. Risk of bias asessment of included interventional studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Sepehr Mamoei 2021 Denmark	High risk	High risk	High risk	High risk	Low risk	Unclear
Laura De Giglio 2019 Italy	High risk	Low risk	High risk	Low risk	High risk	Low risk
Nikhil Satchidanand 2018 USA	Low risk	Low risk	High risk	Low risk	High risk	Low risk
C. Arreola-Mora 2018 Mexico	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Sarah D. Broicher 2018 Switzerland	Low risk	Unclear	High risk	High risk	High risk	High risk
Sarah A. Morrow 2016 Canada	Low risk	Low risk	High risk	Low risk	High risk	Unclear
HB Jensen 2014 Denmark	High risk	High risk	High risk	High risk	High risk	High risk

In a multi-centric study, Mitsikostas et al. enrolled 92 patients with MS and assessed the efficacy of prolonged-release fampridine on cognition (PASAT), fatigue (MFIS), depression (BDI-II), and quality of life (MusiQoL) after 6 months. They found that scores of all items improved 3 and six months after treatment. They found that information processing speed which is a core test in PASAT was improved significantly after 6 months of treatment (6). Significant improvement of information processing speed was reported by Ruck et al. after 9-12 months of treatment with fampridine which was evaluated by PASAT (29). In an open-label study, Bakirtzis et al. evaluated the effects of prolonged-release (PR) fampridine during 6 months of treatment. They investigated significant improvement in walking, cognition (SDMT), and MSIS-29 scores while after 12 months quality of life scores improved significantly, too (21). Jensen et al. reported improvement of SDMT score after one month of treatment with fampridine (28).

In contrast, some other studies which used SDMT or PASAT for cognition assessment did not show a significant improvement after completion of the study period (24, 27, 31). Based on demyelinating axons, high-speed signals are not transmitted properly which leads to impaired information processing speed (32). Information processing speed is the key deficit of cognition in MS which is not always associated with a deficit of other domains (33). On the other hand, learning and memory deficit is not always associated with information processing speed (34, 35). By blocking potassium channels, fampridine improves nerve conduction and faster processing speed as a result (6). Literature shows that fampridine positively affects fatigue and depression in MS (6, 19). Depression and fatigue negatively affect cognition and it should be considered that fampridine improves cognition by improving psychological well-being in MS (22, 36, 37).

Disease duration, physical disability, gray matter atrophy, and disease progression negatively affect cognition in MS (38, 39). To improve cognition, medications such as fampridine, cognitive behavior therapy, psychological well-being (treating depression and fatigue), and sleep quality improvement should be considered (40). This study had some limitations. First, different types of fampridine such as extended-release, slow-release, and prolonged-release were administered. Second, all studies did not have the same follow-up time. Clinical trials with the same follow-up duration, and medication type is recommended. Based on this systematic review, Fampridine has a significant role in decreasing cognitive impairments is MS patients.

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