Original Article

# Investigating the Safety of Fampridine in Patients with Different Stages of Multiple Sclerosis

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## Abstract

**Background:** Fampridine is the only drug approved by the US Food and Drug Administration (FDA) for people with multiple sclerosis (MS) to improve their movement and has exhibited a clinically significant improvement in gait function in a subset of MS patients with Expanded Disability Status Scale (ESDSS) from 4 to 7. Nevertheless, this drug has been reported to possess some adverse effects (AEs) like seizure because of its pharmacological features. The aim of this study was to evaluate the incidence rate of post-medication side effects (SEs) of fampridine in MS patients. **Methods:** This prospective cohort study includes MS patients aged between 18 and 65 years, referred to the neurology clinic of Kashani Hospital from April 2022 to October 2022, all with administration of fampridine (10 mg tablet twice daily according to the product specifications). Safety in these patients was monitored through monthly SEs checklist questions during 6 months of screening. SPSS version 18 was used to analyze the data of this study. **Results:** From 319 participants screened at baseline, 254 patients with MS, including 127 relapsing-remitting multiple sclerosis (RRMS), 101 secondary progressive multiple sclerosis (SPMS), and 26 primary progressive multiple sclerosis (PPMS), were included in the study. The most observed AEs in SPMS and RRMS patients were dry mouth (13.9% vs. 15%) and insomnia (12.9% vs. 11%), respectively. Urinary tract infection (UTI) (11.5%) and stomachache (11.5%) were the most common SEs in PPMS patients. The most severe complication of the patients was back pain, while digestive complications were less severe. Also, insomnia and UTI were the patients' most persistent SEs. **Conclusions:** The drug seems to be safe and well tolerated, as the SEs were mild and transient and they were consistent with most of the previous studies focusing on this medication.

**Keywords:** *Drug adverse reactions, fampridine, multiple sclerosis, safety*

## Introduction

Multiple sclerosis (MS) is a demyelinating and autoimmune disease of central nervous system with clinical manifestations, mainly related to movement, such as weakness, tremors, partial or complete loss of vision, and lack of coordination or unsteady gait.[1] These symptoms may differ significantly from patient to patient and over the course of the disease, depending on the site of the affected neuron fibers.[1-3] In a neurodegenerative disease such as MS, ion channels play a significant role and these are highly considered as potential therapeutic targets.[4,5]

According to the studies, the incidence of MS is rising in different parts of Asia. The overall incidence of MS in East Asian countries such as Japan, Malaysia, and Korea ranged from 0.5 to 0.78 per 100,000, but even these increasing rates cannot still reach the high incidence regions in western Asia like Iran (3.4 per 100,000) or other areas, like the United States and some parts of Europe.[6]

Gait problems are one of the most common difficulties that these patients face, making them less independent in life and have a loss of movement-related quality of life.[7] Muscle weakness and spasticity cause MS patients in need of ambulatory aid even in the first year of disease onset.[8] In spite of the fact that there is no cure for MS, fortunately, there has been such great progress with therapeutic methods and treatments as various drug groups are available.[9] However, the treatment methods may be dramatically different in these patients and are even relatively different in patients with similar disorders such as neuromyelitis optica spectrum disorder.[2]



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Among these drugs, fampridine was approved by the US Food and Drug Administration (FDA) about 12 years ago due to the effectiveness and safety results of a large-scale study performed by Goodman *et al*.[10,11] and considered effective and safe as it only exhibited transient and moderate adverse events in future studies.[12] This is the only and first drug to ameliorate patients' movement and walking ability.[8,11,13] Owing to its pharmacological properties, such as blocking the potassium channels in neurons, this lipid-soluble drug can enhance the electrical conduction in damaged neurons, leading to an increase in walking speed.[14] Nevertheless, this may induce epileptogenic conditions in patients, which is the most worrying adverse effect (AE) as well as renal impairment.[13]

As, to our knowledge, there are few studies focusing on prolonged and short-term side effects (SEs) of this drug in MS patients, we evaluated the incidence rate of post-medication SEs of fampridine among these patients.

## Methods

### Participant and study design

This prospective study includes MS patients aged between 18 and 65 years, referred to the neurology clinic of Kashani Hospital from April 2022 to October 2022, all with the prescription of fampridine (10 mg tablet twice daily according to the product specifications). After a detailed review of the clinical records, the patients were selected and asked to answer the questions of a three-part checklist. The first part of the checklist obtained the demographical data and period of drug consumption. The second part was designed considering a list of AEs consistent with previous studies reporting fampridine medical SEs. It contained SEs such as insomnia, vertigo, urinary and bladder infection, headache, paresthesia, seizure, nausea, constipation, dyspepsia, asthenia, backache, acute relapse, nasopharyngitis, mental and cognitive disorders (including but not limited to depression and anxiety), walking dysfunctions, xerostomia, and abdominal pain. The third part included some other SEs reported by the patients themselves. The safety profile in these patients was monitored through monthly SEs checklist questions during 6 months of screening. Patients who could not continue taking fampridine for more than 1 month due to severe AEs or drug intolerance were not analyzed in this study, and their descriptive data and the reasons for their withdrawal were recorded.

### Inclusion and exclusion criteria

The inclusion criteria established in this study were as follows: age between 18 and 65 years and consumption of fampridine (Dalfyra 10 mg, Cinnagen, Tehran, Iran). Patients using metformin, cimetidine, and quinidine were not included in the study due to the contraindication of these drugs with fampridine. The exclusion criteria included patients diagnosed less than 6 months before the initiation of the project, pregnant patients, and patients with comorbidities such as hypertension, arrhythmia, heart, and renal impairment [glomerular filtration rate < 60 mL × $min^{-1}$ × (1.73 $m^2$) – 1]. McDonald's diagnostic criteria for MS were used to diagnose MS. The degree of the patient's disability was determined by the Kurtzke Expanded Disability Status Scale (EDSS).[15] In addition, we classified the disease course as primary progressive MS (PPMS), secondary progressive MS (SPMS), and relapsing-remitting MS (RRMS).[16]

### Statistical analysis

The data were analyzed using SPSS software version 18. Descriptive statistics was reported by means ± standard deviation (SD) for normal quantitative variables, median (interquartile range) for non-normal quantitative variables, and frequency (percent) for qualitative variables.

## Results

### Overview

At the start of the study, 319 patients who met the inclusion criteria were included. Two hundred fifty-four patients finally tolerated the medicine and were examined during follow-ups of the study. The demographic data and the significant fampridine SEs during the study are reported in Table 1. The mean age was 42.51 (SD = 9.28), ranging from 20 to 69 years and 179 patients (70.5%) were female. RRMS was diagnosed in 127 (50%), SPMS in 101 (39.8%), and PPMS in 26 (10.2%) patients. The most prevalent SEs of fampridine were dry mouth (13.4%), insomnia (11%), and urinary tract infection (UTI) (10.8%).

**Table 1: Patients' characteristics and the frequency of fampridine SEs. EDSS at the onset of the disorder**

| Characteristics | Value | |
|---|---|---|
| Age; mean (SD) | 42.51 (9.28) | |
| EDSS at onset; median (IQR) | 2 (1) | |
| Current EDSS; median (IQR) | 3 (2) | |
| Female/male | 179/75 | |
| MS type; *n* (%) | RRMS | 127 (50) |
| | SPMS | 101 (39.8) |
| | PPMS | 26 (10.2) |
| UTI; *n* (%) | 27 (10.8%) | |
| Insomnia; *n* (%) | 28 (11.0%) | |
| Vertigo; *n* (%) | 16 (6.4%) | |
| Headache; *n* (%) | 15 (5.9%) | |
| Paresthesia; *n* (%) | 2 (0.8%) | |
| Nausea; *n* (%) | 8 (3.1%) | |
| Constipation; *n* (%) | 15 (5.9%) | |
| Dyspepsia; *n* (%) | 6 (2.4%) | |
| Backache; *n* (%) | 6 (2.4%) | |
| Nasopharyngitis; *n* (%) | 3 (1.2%) | |
| Memory impairment; *n* (%) | 7 (2.8%) | |
| Walking disorder; *n* (%) | 6 (2.4%) | |
| Dry mouth; *n* (%) | 34 (13.4%) | |
| Stomachache; *n* (%) | 9 (3.5%) | |

### Findings on potential SEs

The frequency of fampridine SEs by MS type is reported in Table 2 and Figures 1–3. The most frequently observed SEs among patients with RRMS and SPMS were dry mouth (15% vs. 13.9%) and insomnia (11% vs. 12.9%), respectively. Also, UTI (11.5%) and stomachache (11.5%) were more frequent among patients with PPMS [Figure 3].

### Intensity and duration of SEs

The most intense SE reported by individuals suffering from MS who were treated with fampridine was backache, followed by walking disorders, and the least intense ones were stomachache, nausea, and headache.

The commented paragraph should be replaced with this paragraph "Overall, insomnia and UTI were the most persistent side effects reported in patients, lasting an average of 76.36 days. The duration of paresthesia, nasopharyngitis, and walking disorders was not assessed."

The data of 65 patients (20.3%) initially included in the study was not statistically analyzed. These patients did not tolerate the medication for different causes and were withdrawn from the study because the duration of their use was less than 1 month. The demographic and clinical information of these patients, along with the reasons for drug discontinuation, are available in Table 3.

Of these 65 patients, there were 47 RRMS, 16 SPMS, and 2 PPMS. In the RRMS and SPMS groups, lack of efficiency and gastrointestinal symptoms were the most common causes of drug discontinuation, with 40.42% and 62.5%, respectively, while gastrointestinal symptoms and recurrent infection were the only causes of drug discontinuation in the PPMS group.

**Table 2: Frequency of fampridine SEs by MS type**

| | RRMS (*n*=127) | SPMS (*n*=101) | PPMS (*n*=26) |
|---|---|---|---|
| UTI; *n* (%) | 11 (8.9%) | 13 (12.9%) | 3 (11.5%) |
| Insomnia; *n* (%) | 14 (11.0%) | 13 (12.9%) | 1 (3.8%) |
| Vertigo; *n* (%) | 5 (4.0%) | 9 (8.9%) | 2 (7.7%) |
| Headache; *n* (%) | 7 (5.5%) | 7 (6.9%) | 1 (3.8%) |
| Paresthesia; *n* (%) | 2 (1.6%) | 0 (0.0%) | 0 (0.0%) |
| Nausea; *n* (%) | 1 (0.8%) | 6 (5.9%) | 1 (3.8%) |
| Constipation; *n* (%) | 12 (9.4%) | 3 (3.0%) | 0 (0.0%) |
| Dyspepsia; *n* (%) | 3 (2.4%) | 1 (1.0%) | 2 (8.0%) |
| Backache; *n* (%) | 2 (1.6%) | 3 (3.0%) | 1 (3.8%) |
| Nasopharyngitis; *n* (%) | 2 (1.6%) | 1 (1.0%) | 0 (0%) |
| Memory impairment; *n* (%) | 2 (1.6%) | 4 (4.0%) | 1 (3.8%) |
| Walking disorder; *n* (%) | 2 (1.6%) | 3 (3.0%) | 1 (3.8%) |
| Dry mouth; *n* (%) | 19 (15.0%) | 14 (13.9%) | 1 (3.8%) |
| Stomachache; *n* (%) | 3 (2.4%) | 3 (3.0%) | 3 (11.5%) |

## Discussion

The findings of this study suggest that fampridine administration has no serious or permanent AEs in patients with different types of MS. In autoimmune inflammatory diseases like MS, a sudden shift in neurological function happens, and these acute inflammatory demyelination

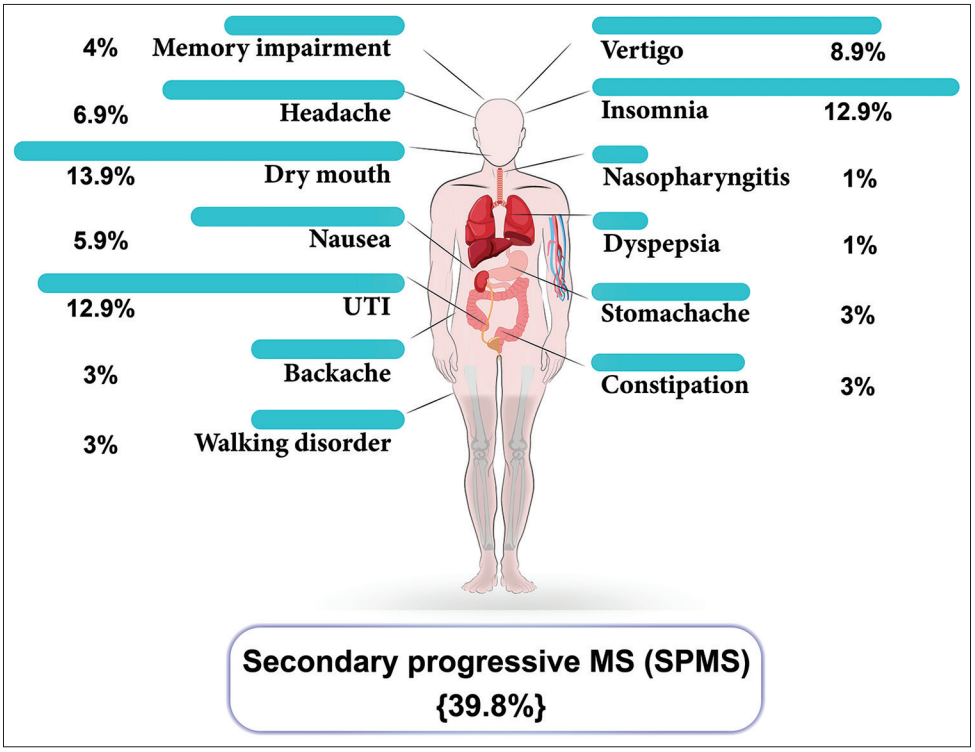


**Figure 1: The frequency of fampridine SEs in SPMS patients**

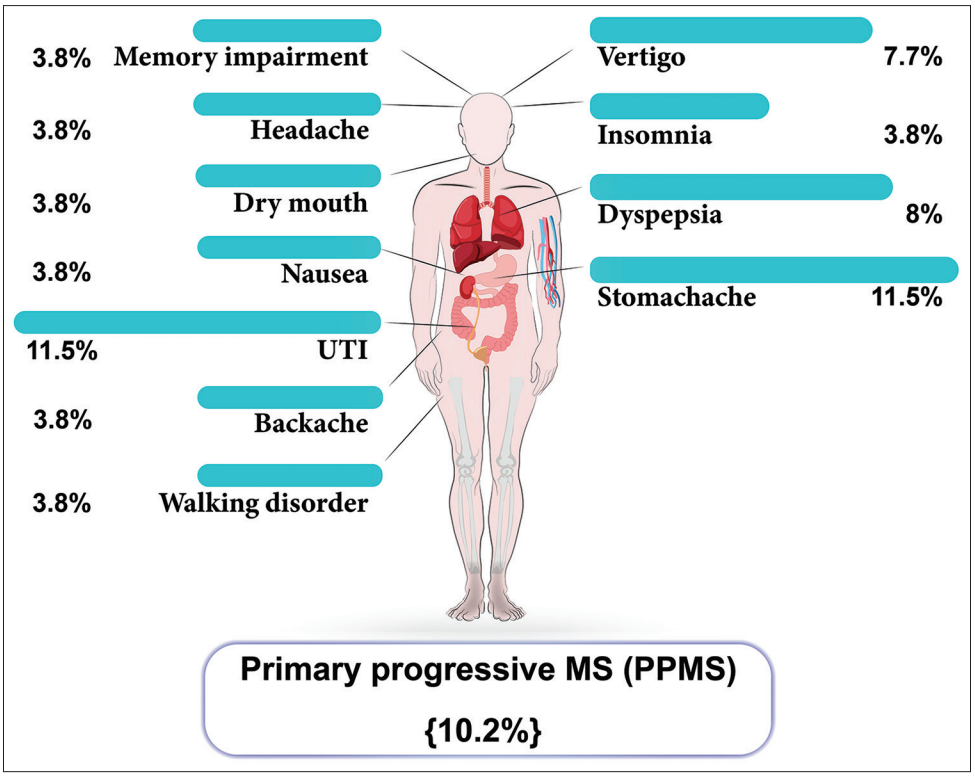


**Figure 2: The frequency of fampridine SEs in PPMS patients**

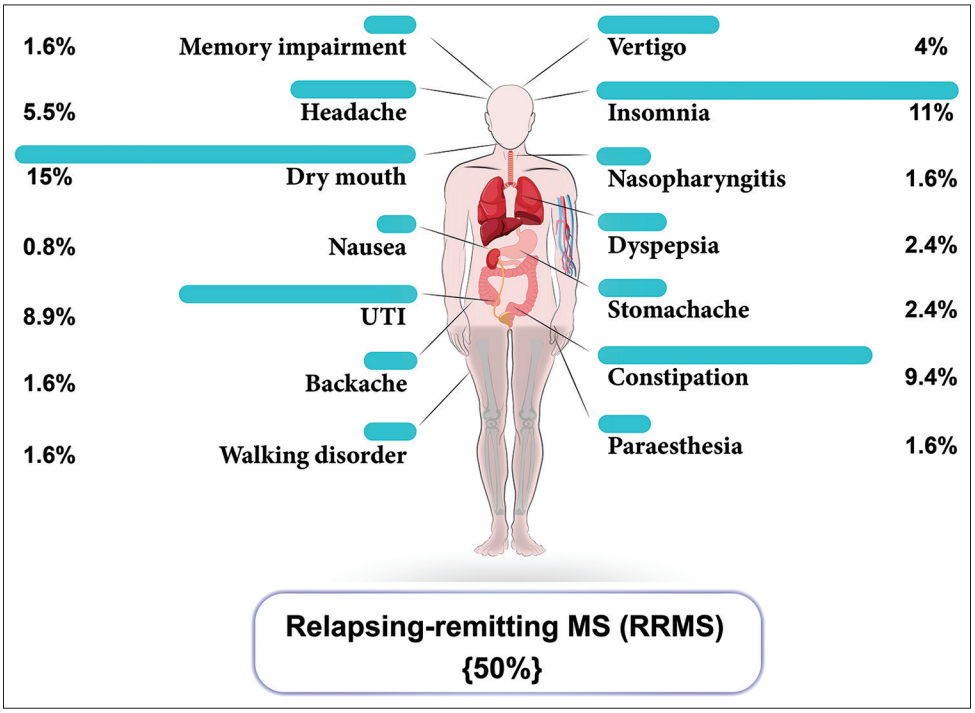


**Figure 3: The frequency of fampridine SEs in RRMS patients**

situations, clinically called relapses, develop many clinical abnormalities by affecting highly myelinated regions of the nervous system such as the spinal cord, optic nerve, brain stem, and cerebellum.[17] Among this clinical manifestation, gait dysfunction is one of the most ubiquitous, impactful, and life-limiting consequences, with a wide range of contributing factors such as sensory changes, lower extremity weakness or spasticity, and cerebellar ataxia.[18,19] These clinical symptoms directly correlate with demyelination, the pathologic hallmark of

**Table 3: Patient' characteristics and the reason for discontinuing fampridine**

| | RRMS | SPMS | PPMS |
|---|---|---|---|
| Number of patients (% from total subgroup participants) | 47 (47%) | 16 (13.67) | 2 (7.14) |
| Age; mean (SD) | 44.63 (6.8) | 45.23 (7.8) | 43.52 (2.3) |
| Female/male | 35/12 | 12/4 | 2/0 |
| EDSS at onset; median (IQR) | 1.5 (2) | 1.5 (2) | 3.5 (1.5) |
| Current EDSS; median (IQR) | 0.0 (2) | 2.5 (1) | 3.0 (1) |
| Discontinuation reasons | | | |
| Gastrointestinal symptoms (%) | 13 (27.65%) | 10 (62.5%) | 1 (50%) |
| Dysphoria (%) | 10 (21.27%) | 3 (18.75%) | 0 (0%) |
| Seizures (first onset) (%) | 2 (4.25%) | 0 (0%) | 0 (0%) |
| Trigeminal neuralgia (%) | 1 (2.12%) | 0 (0%) | 0 (0%) |
| Lack of efficiency (patient's view) (%) | 19 (40.42%) | 3 (18.75%) | 0 (0%) |
| Recurrent infection (%) | 2 (4.25%) | 0 (0%) | 1 (50%) |

MS, which causes acute functional changes by altering the impulse conduction in axons. As it was mentioned earlier, this conduction defect is raised by alterations in function and contribution of voltage-gated ion channels.[4] There are a variety of voltage-gated channels in axons that carry out a vital function in impulse conduction. Voltage-gated $Na^+$ channels ($Na_v$) are mostly located in non-myelinated parts (node of Ranvier and initial segments) of a normal axon, which is initially responsible for producing an action potential. And voltage-gated $K^+$ channels ($K_v$) in nodal and juxtaparanode regions covered by the myelin sheet play a role in neural excitability.[20] Blockade of $Na^+$ channels during relapses due to cytokine release or antibody attachment leads to a high level of intracellular $Na^+$. This situation leads to the failure of the $Na^+/K^+$ ATPase pump due to lack of ATP and this failure exacerbates the intracellular $Na^+$ aggregation, causing the $Na^+/Ca^{2+}$ exchanger to act reversely. The extra intracellular $Ca^{2+}$ initiates apoptosis and axon degeneration[4,21] [Figure 4]. In addition, the demyelination exposes the $K^+$ channels and leads to $K^+$ leakage. As a result, it repolarizes the cell and decreases the neural excitability. The overall impact is neuromuscular communication impairment as it is harder to initiate an action potential[4,22] [Figure 4]. In all parts of the body, ion channels have been suggested to have attractive therapeutic potentials, and insights into the role of these channels in neurons have led to the development of new high-efficacy drugs.[23]

Of particular note, studies have exhibited improvements in the gait and neurological function of MS patients treated with fampridine.[24] Other studies have recently shown that prolonged-release fampridine has significant positive effects on cognition, and depression in MS patients, and improves quality of life in these patients.[25,26] Fampridine, with the generic name of dalfampridine, is an FDA-approved broad-spectrum lipophilic drug for MS patients, sold under the name of Ampyra in the United States and Fampyra in Europe, Canada, and Australia.[8,9] This drug has demonstrated the therapeutic effects on motor dysfunction in patients with MS, by blocking the exposed potassium channels on demyelinated axons as its main pharmacological property. However, it can relieve the conduction blocks that result in the facilitation of neuromuscular and synaptic transmission and it can also affect the voltage-activated calcium channel independent of potassium channels.[27,28] All these pharmacological features increase the amplitude of the action potential and this may increase the risk of seizures. The gastrointestinal tract rapidly absorbs the orally administered dalfampridine. Complete elimination of this drug and its metabolites is carried out by the kidney, making this drug harmful for patients with significant kidney diseases.[14]

In a small randomized trial performed on eight MS patients with motor deficits, immediate-release fampridine was evaluated in high serum and low serum concentrations. All patients with high serum concentration (>60 ng/mL) experienced SEs. One patient showed a grand ma1 seizure at a serum fampridine level of 104 ng/mL and another patient developed an acute confusional episode at a serum concentration peak of 114 ng/mL.[29] In another trial performed by Schwid *et al*.,[30] on 10 MS patients, no serious SE occurred and only patients with serum concentration >60 ng/mL exhibited improvements. Comparing these results suggests a narrow margin between therapeutic concentration and toxic concentration of fampridine which leads to AEs. Goodman *et al*.[31] performed a phase II multicenter randomized trial in 2008 to evaluate the efficacy and SEs of three different doses of fampridine in patients with MS. In this dose-comparison study, 206 MS patients received fampridine 10, 15, or 20 mg or placebo. Severe and serious SEs were seen more in the high-dose group (20 mg) and included UTI (16%), headache (14%), and paresthesia (14%). Nevertheless, no clear dose-related increase was seen in most of the SEs.[31] In a dose-raging study, 25 MS patients received 10–40 mg of fampridine. Dizziness, paresthesia, insomnia, asthenia, tremor, nausea, and headache were the most common SEs and five subjects were excluded from the trial at doses greater than 25 mg due to convulsions in two patients at doses of 30 and 35 mg.[32] Two phase III trials in 2009

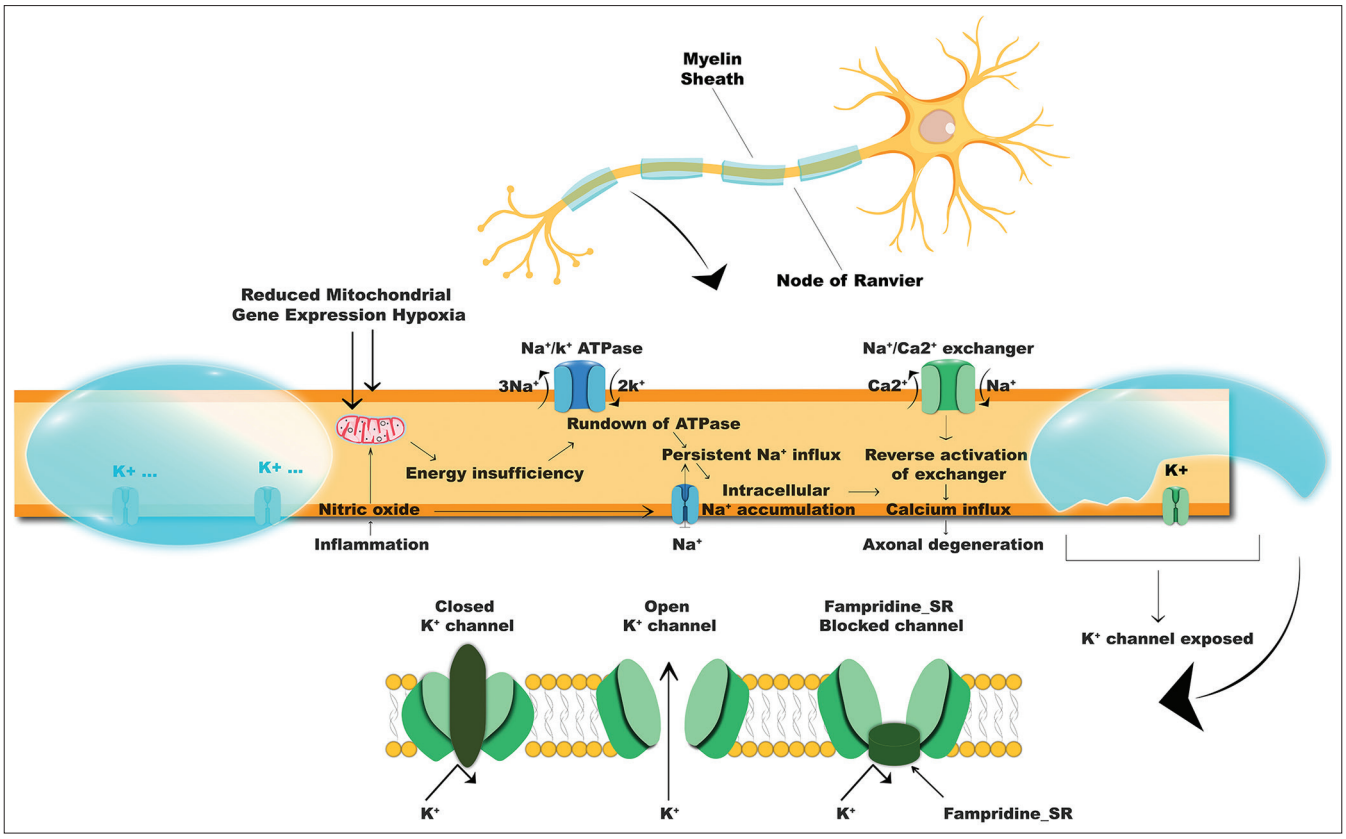


**Figure 4: Role of ion channels in axonal degeneration in MS and downstream effects of fampridine. A cascade of events like mitochondrial failure and persistent $Na^+$ channels lead to high levels of intracellular $Na^+$. This situation causes the $Na^+/Ca^{2+}$**

and 2010 were performed by Goodman *et al.*,[33] leading to FDA approval of fampridine.[10] In the first parent study, 11 patients (5%) of the fampridine-treated group were withdrawn from the study due to SEs such as sepsis, ankle fracture, balance disorder, confusion state, headache, dizziness, and anxiety. Moreover, 16 patients (7%) experienced one or more serious adverse events (UTI and MS exacerbation were most common). A focal seizure occurred and it was judged as possibly related to fampridine treatment. Besides, the death of a patient one week after the study completion was considered to be unrelated to the treatment.[33] In the second parent trial, five patients (4.2%) in the fampridine-treated group experienced one or more serious AEs. The fampridine-treated group experienced events including UTI (17.5%), fall (11.7%), insomnia (10%), and headache (9.2%). Other AEs like asthenia, dizziness, nausea, back pain, balance disorder, upper respiratory tract infection, arthralgia, nasopharyngitis, and paresthesia were also observed in the fampridine-treated group.[10] The long-term evaluation of the safety and efficacy of fampridine, which was published in 2015, was almost consistent with the two previous parent trials.[34] In a 5-year (from 2010 to 2015) post-marketing study on 107,000 patients treated with fampridine in the United States, the most common AEs were dizziness (3.7%), insomnia (3.2%), balance disorder (3%), fall (2.4%), headache (2.4%), nausea (2.1%), and UTI (2%). Rare anaphylactic reactions and drug hypersensitivity reactions were seen in some patients as serious AEs.[35] No epileptic condition was seen in both ENHANCE and MOBILE trial.[36,37] This study provides additional evidence on SEs of fampridine in MS patients. Nevertheless, it has a number of limitations. First, over 70% of our study population consisted of women, which may hamper the generalizability of the findings to settings and locations where a more balanced distribution of MS between the two sexes are observed. Second, the fact that a self-administering checklist was utilized to obtain data renders our findings prone to a number of forms of bias. As such, future research is needed to further illuminate the safety and efficacy of fampridine in individuals with MS.

## Conclusions

In this study, we compared the SEs of fampridine in patients with different types of MS. The drug seems to be safe and well tolerated, as the SEs were mild and transient and they were similar with most of the previous studies focusing on this drug. However, more controlled studies with larger scale and longer follow-ups will be needed to further evaluate the AEs of fampridine in patients with MS.

### Declaration

The Isfahan University approved this study of Medical Sciences protocol with an ethic code (IR.MUI.MED.

REC.1400.001). All patients entered the study by filling out a written consent form. No authors declared any conflict of interest. O.M. and V.Sh. were involved in study conceptualization, A.A.S. and S.B. in data curation, A.A.S. in analysis, S.V. in study investigation, O.M., S.V., A.Sh., and S.B. in methodology, O.M., V.Sh., and S.B. in project administration, O.M. and V.Sh. in supervision, O.M. and V.Sh. validation and O.M., M.F., and S.B. were involved in writing, review, and editing. This study has not received any financial funding. The study data can be sent upon request.

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### Conflicts of interest

There are no conflicts of interest.

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