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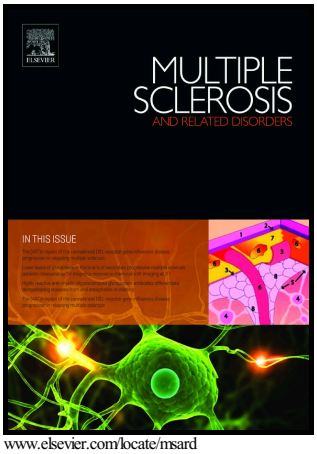


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# Sulbutiamine shows promising results in reducing fatigue in patients with multiple sclerosis

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**ABSTRACT**

**Background**

Fatigue is the most frequent and often debilitating symptom for patients with multiple sclerosis (MS). There are no available effective therapies for fatigue associated with MS, and it is unclear whether a successful therapy of MS leads to clinical improvement. Sulbutiamine is a lipophilic compound that crosses the blood–brain barrier more readily than thiamine and increases the levels of thiamine and thiamine phosphate esters in the brain. Whereas several clinical trials have demonstrated the beneficial effects of sulbutiamine in patients with asthenia, there have been no reports on the effects of sulbutiamine on fatigue in patients with MS.

**Objectives**

Our study was designed to evaluate the short-term effects of sulbutiamine on fatigue in patients with MS.

**Methods**

Patients were included if fatigue was one of their three predominant symptoms. They were required to have a total score on the Fatigue Impact Scale (FIS) of >20, and on the Beck Depression Inventory of<17, and no relapse in the last 3 months prior to onset of the study. Patients were advised to receive 400mg orally of sulbutiamine once daily for two months. The outcome of the study was in the changes of FIS.

**Results**

Twenty-six patients with MS (18 females and 8 males) were selected. The patients were 18 to 57 years of age (mean:37,2). The average score of Expanded Disability Status Scale (EDSS) of the patients was 2,71. A significant number of the subjects who were on some kind of disease modifying treatment (DMT) demonstrated obvious improvement in their total FIS scores, whereas none of the subjects who were not on any DMT improved (13/23 vs. 0/5). The average fatigue score was 77 (SD:30,5) at the baseline and 60,5 (SD:29,7) on Day 60, respectively. Sulbutiamine intake resulted in a significant reduction on the total score of FIS and on all three subscales assessing physical, cognitive, and psychosocial functioning (all p-values<0,01). There were no serious adverse events.

**Conclusions**

Sulbutiamin appears to be effective in treating fatigue in MS; particularly in patients who were on some DMT, but not on those who were not. It is well-tolerated by all. This observation may encourage further evaluations of the efficacy of sulbutiamine on fatigue in MS.



## 1. Introduction

Multiple sclerosis (MS) is a chronic and inflammatory neurodegenerative disease which afflicts more than 2 million people in the world. It causes a wide range of symptoms, of which fatigue is one of the most frequent and disabling. Fatigue may affect up to 92% of the patients living with MS and has a major impact on quality of life (Fisk et al.,1994a; Branas et al., 2000). Moreover, it is shown that fatigue in MS persists over time once it appears (Tellez et al., 2006). Most of the patients with MS report that their fatigue is severe (Hadjimichael et al., 2008). Clinically, it presents as exhaustion, loss of energy, daytime somnolence, or exacerbation of symptoms (Vucic et al., 2010). Fatigue in MS can be differentiated from fatigue in normal individuals because it worsens with heat, interferes with physical functioning and performance, prevents sustained physical activity, comes on easily and causes frequent problems (Branas et al., 2000; Krupp et al., 1998). The mechanism of fatigue in MS is still unknown and could be due to lesions of cortical or subcortical pathways involving motor cortex and basal ganglia, autonomic dysfunction, hypothalamic pituitary adrenal axis dysregulation and/or endocrine disturbances (Gottschalk et al., 2005; Nourbakhsh et al., 2016; Finke et al 2015; Flachenecker et al 2003; Induruwa et al., 2012). In the light of this, elucidation of the pathogenesis of fatigue occurring with MS and the development of effective therapies for its relief are important goals for neurologists.

Unfortunately, there are no available effective therapies for fatigue associated with MS. Several drug treatments have been evaluated for fatigue in patients with MS but none found to be effective (Tur C, 2016).

Sulbutiamine is a synthetic compound composed of two thiamine (vitamin B1) molecules fixed with a disulfide bond which provides its lipophilic properties. Accordingly, it crosses the blood–brain barrier more readily than thiamine and increases the levels of

thiamine and thiamine phosphate esters in the brain (Bettendorff et al., 1990). Sulbutiamine is postulated to be effective for the treatment of asthenia and chronic fatigue (Layzer, 1990). The aim of this retrospective study was to evaluate the effect of sulbutiamine on the severity of fatigue in patients with MS.

## 2. Methods

We analyzed patients with MS who were orally administered sulbutiamine 400mg once daily by using our medical records. Data were extracted from our outpatient MS clinic where all patients with MS suffering from fatigue are being evaluated by fatigue, depression and anxiety scales before and after the onset of any treatment. The timing to assess the efficacy and tolerability of each treatment method is established on each method's peculiar characteristics.

### *2.1. Design*

This was a retrospective observational study. The primary objective was to quantify the effects of sulbutiamine on fatigue in patients with RRMS by using the overall and three subscales of the FIS.

### *2.2. Procedure*

The fatigue impact scale (FIS) and its modified versions are multidimensional scales and have proven to be robust tools in investigating the impact of fatigue on the quality of life of various groups of patients, including those with MS (Metz et al. 2004; Calabrese et al. 2010; Sumowski and Leavitt, 2014; Jongen et al. 2014). It is a self-report questionnaire consisting of 40 statements in which patients describe possible manifestations of fatigue, each of which is scored 0 (no problem) to 4 (extreme problem), providing a continuous scale of 0–160. The FIS tool is composed of three subscales that describe how the fatigue impacts cognitive (10 items), physical (10 items) and psychosocial functioning (20 items) (Fisk et al., 1994b; Armutlu et al., 2007).

Depression was assessed using the Beck Depression Inventory (BDI-II), a standardized 21-item measure of cognitive, affective, and somatic symptoms of depression available in Turkish (Kapçı et al., 2008).

The main criteria defining responder vs. non-responder was the change in the overall score of FIS between the study entry and Day 60. Patients who had a decline in the overall score on FIS by 24% or less were considered as 'non-responders', whereas those had a decline between 25-40% as 'responders' and those who had more than 40% are 'markedly good responders' when compared with baseline overall FIS scores.

### *2.3. Patients*

We included patients if they were 18-60 years old, diagnosed with RRMS according to 2010 McDonald criteria, fatigue was one of their three predominant symptoms, had voluntarily completed FIS and BDI-II at the initial visit, and FIS at any follow-up visit within 60–66 days of the initial visit (Polman et al., 2011).

They were required to have a total score on the FIS>20 and on BDI-II<17 and no relapse within the last 3 months prior to onset of the study. Patients with ferritin levels under 20ng/ml; thyroid, liver, pancreatic and inflammatory bowel disorders; diabetes, any addiction including cigarettes, had had a relapse within the last 3 months or a total score of BDI-II >16 before using sulbutiamine were excluded from the study.

All patients provided fully informed written consent and the study was approved by the local ethics committee.

*2.4. Statistical Analysis*

Descriptive statistics for continuous demographic data were taken as mean, standard deviation, minimum and maximum. The descriptive statistics for the data in the categorical structure were given as number and percentage. After performing the normal distribution control with Kolmogorov-Smirnov test for the scale scores, the difference between the pre-test and the post-test was evaluated by Paired t test in terms of total score and subscale scores. The change in pre-test and post-test scores for each question was assessed using the McNemar-Bowker test. The difference in treatment response between the groups was compared in terms of mean change (%) in the FIS score. P values of <0.05 were regarded as significant.

**3. Results**

A total of 234 patients with MS and fatigue were screened for the study. Of those screened, 209 (89,3%) did not meet the fatigue eligibility criteria. In total 26 patients aged 18-57 (mean:37,2) with MS (18 females and 8 males) were eligible for the study. The body mass index (BMI) of all patients was between 18.6 and 28,1 (mean:23,9). The Expanded Disability Status Scale (EDSS) of patients ranged from 1 to 5.5 (mean:2,71). Eight patients were current users of fingolimod, six of beta-interferons, six of glatiramer acetate (GA), and one of azathioprine. Five patients were not receiving any disease modifying treatment (DMT) with proven efficacy, all due to personal preference (untreated patients) (Table 1).

The average total FIS score of the patients was 77 (SD:30,5) and 60,5 (SD:29,7) at baseline and on Day 60, respectively ( p>0,001). Regarding the FIS subscales these values were 19,37 (SD:9,36) and 15 (SD:8,86) for cognitive; 30,6 (SD:9) and 20,36 (SD:8,56) for physical; 35,9 (SD:18,39) and 27,93 (SD:18,81) for psychosocial. (p>0,001for physical and psychosocial subscales; p = 0,001 for cognitive subscale). The recovery in the average total FIS score of the patients who were current users of DMTs was significantly more than the 'untreated' patients (p=0,032). No difference was found between the average EDSS scores of treated (using a DMT) and untreated patients.

We found for individual subjects that 23/26 had improved overall FIS scores over a two-month time period whereas 1/26 remained the same and 2/26 worsened. In total half of the patients ranked among either in the 'markedly good responder' or the 'responder' group (9/26 in the markedly good, and 4/26 in the responder group). The other half fell into the 'non-responder' group.

None of the 5 patients who were in the 'untreated group' responded to sulbutiamine. Of these five patients one was one of the two in the group who had an increase in the total FIS score when compared with baseline. Moreover, another patient of these five was the only one whose total score remained the same at the end of two months.

No correlation was found between the EDSS scores, the total number of MS attacks, the BMI and being a responder (all p values>0,05). None of the patients experienced adverse effects related to sulbutiamine. The overview of summary statistics of the respective overall FIS and subscale scores are shown in Table 2.

**4. Discussion**

Fatigue is perhaps the most common symptom for patients with MS and the current literature shows that there are no available effective drugs for fatigue associated with MS. In the current study, sulbutiamine intake resulted in a significant reduction of the overall score of FIS and all three subscales assessing physical, cognitive, and psychosocial functioning. Moreover, more than one-third of the patients had obvious reductions of fatigue symptoms on an individual basis. We did not observe any serious adverse effect in any of the patients.

An in vitro study showed neuroprotective evidence of sulbutiamine on rat hippocampal neurons under oxygen–glucose deprivation. It increased neuronal viability and enhanced excitatory synaptic transmissions and intrinsic neuronal membrane input resistance in a concentration-dependent manner. Moreover, researchers postulated that it probably protects the initiation of oxidative stress (Kwag et al. 2011). In another study, sulbutiamine was shown to prevent harmful effects of dizocilpine on the working memory in rats (Bizot et al., 2005).

To date, there are no evident data showing favorable effects of sulbutiamine in any patient group with chronic fatigue, even though it is frequently used as over-the-counter medicine for fatigue in many chronic diseases. However, sulbutiamine showed beneficial effects in an open label trial involving 1772 patients with postinfectious disease and asthenia, particularly in the subgroup of patients with symptoms associated with the central nervous system (Shah et al., 2003).

A recent proposal about fatigue in MS is the imbalance of dopamine in the MS brain. There is an increasing number of structural and functional neuroimaging studies supporting this hypothesis. Moreover, methylphenidate, a potent dopamine reuptake inhibitor, is shown to reduce fatigue symptoms in patients with traumatic brain injury and cancer (Dobryakova et al., 2015). On the other hand, sulbutiamine is shown to have regulatory effects on dopaminergic receptors in the rat brain (Trovero et al., 2000; Yamashita et al., 1993; Bettendorf et al., 1990). Thus it is possible that sulbutiamine alleviated fatigue via its regulatory effect on dopamine metabolism in our patient group.

One of the interesting findings of the current study was the occurrence of improvements in fatigue only in patients who were using a DMT, but not those who were untreated. None of the five patients who were not using a DMT responded to sulbutiamine. Although the 3 major treatment drugs in the current study (fingolimod, beta-interferons and GA) are known to have different mechanisms of action, this finding brings up the question whether or not sulbutiamine could be only effective or more effective in patients who receive DMTs. Nonetheless, one should keep in mind the extremely small number of patients in the untreated group and many other drawbacks of this study when interpreting this result. The other results of this study should also be considered in the context of this study's limitations. First, as this was an observational study without a randomized control group, it is not possible to eliminate the placebo effect regarding the efficacy of sulbutiamine. Instead, we compared each patient with his/her baseline and Day 60 values. Another drawback of our study was its length of time which might not be long enough to evaluate the potential side effects and possibly efficacy of a drug. Moreover, the study group consisting of 26 patients is relatively small to achieve more reliable results, particularly when comparing subgroups. Furthermore, although FIS is a detailed and proven measurement method for fatigue, application of an appropriate 'quality of life scale' could have consolidated our results.

Nevertheless, our study was the first to evaluate the possible benefits of sulbutiamine in patients with MS and fatigue. Furthermore, our group consisted of homogeneous patients regarding MS type and none had a comorbidity that could affect the results of the study including low ferritin levels or anemia; cigarette smoking; liver, thyroid or inflammatory bowel disease; diabetes or depression.

**5. Conclusion**

Although it had many major drawbacks, this is the first time a study to show a positive effect of sulbutiamine on fatigue in MS. Our study has revealed new data regarding the beneficial effects of a short-term treatment of sulbutiamine in patients with MS who suffered from fatigue. Considering the negative impact of fatigue on the quality of life in MS patients, it is crucial to further confirm these data in long-term, placebo-controlled and multicentre trials.

Conflict of interest

We have nothing to disclose



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**Table 1.** Baseline clinical characteristics of patients enrolled in this study.

| **Characteristic** | **Patients N=26** |
|---|---|
| Mean Age (min-max) | 37,2 (18-57) |
| Gender Female-n(%) | 18 (69,2) |
| Mean BMI (min-max) | 23,9 (18,6-28,1) |
| Mean EDSS score (min-max) | 2,71 (1-5.5) |
| Mean no. of relapses | (1-8) |
| Treatment status (no. of patients) | Fingolimod:(8);<br>ß interferons:(6)<br>Glatiramer acetate:(6)<br>Azathiopurine:(1)<br>No DMT:(5) |

BMI:Body-Mass Index; EDSS: The Expanded Disability Status Scale; DMT: Disease Modifying Treatment

**Table 2.** The overall and subscale total scores at baseline and at Day 60 as assessed by FIS.

| | **Total Score at baseline (SD)** | **Total Score at Day 60 (SD)** | **p value** |
|---|---|---|---|
| Mean Total FIS | 77(30,5) | 60,5(29,7) | <0,001 |
| Mean Cognitive Subscale | 19,73(9,36) | 15(8,86) | =0,001 |
| Mean Physical Subsscale | 30,6(9) | 20,36(8,56) | <0,001 |
| Mean Psychosocial subscale | 35,9(18,39) | 27,93(18,81) | <0,001 |

FIS:Fatigue Impact Scae; SD:Standard Deviation; min:minimum value; max.maximum value

HIGHLIGHTS

*Fatigue is the most frequent and often debilitating symptom for patients with MS
*There are no available effective drugs for fatigue associated with MS
*Sulbutiamine increases the levels of thiamine and its phosphate esters in the brain
*In the current study sulbutiamine intake reduced fatigue symptoms in patients with MS
* This is the first study to show a positive effect of sulbutiamine on fatigue in MS