

# Positive correlation between functional disability, excessive daytime sleepiness, and fatigue in relapsing–remitting multiple sclerosis

Correlação positiva entre incapacidade funcional, sonolência excessiva diurna e fadiga na forma recorrente-remitente da esclerose múltipla

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## ABSTRACT

Sleep disorders in patients with multiple sclerosis have various causes and interfere with daytime wakefulness. This study assessed the correlation between fatigue, excessive daytime sleepiness and level of disability. **Method:** Retrospective review of medical records from patients with multiple sclerosis to collect data on severity of fatigue, disability, daytime sleepiness, and depression. From 912 medical records reviewed, 122 reported daytime sleepiness: 67% had relapsing remitting, 12% had primary progressive, and 21% had secondary progressive. **Results:** In 95% of the patients with relapsing remitting who complained of daytime sleepiness and fatigue, association was found between these symptoms and neurological disability. Patients with relapsing remitting who complained of daytime sleepiness and fatigue also experienced depression ( $p = 0.001$ ). No association between fatigue, excessive daytime sleepiness, depression, and disability was found in patients with progressive disease. **Conclusion:** In relapsing remitting, there is correlation between functional disability, excessive daytime sleepiness and fatigue, a finding not confirmed in primary progressive and secondary progressive form.

**Keywords:** multiple sclerosis; disabled persons; fatigue; disorders of excessive somnolence.

## RESUMO

Os distúrbios do sono em pacientes com esclerose múltipla são multifatoriais e interferem no alerta diurno. O objetivo deste estudo foi verificar a correlação entre a fadiga, sonolência excessiva diurna e nível de incapacidade. **Método:** Estudo retrospectivo de prontuários de pacientes com esclerose múltipla, onde foram coletados dados sobre gravidade da fadiga, nível de incapacidade, sonolência diurna e depressão. Dos 912 prontuários analisados, 122 apresentaram queixa de sonolência excessiva, divididos 67% forma recorrente-remitente; 12% forma primariamente progressiva; 21% forma secundariamente progressiva. **Resultados:** 95% dos pacientes recorrente remitente apresentaram sonolência excessiva diurna e fadiga, foi observada associação entre estes sintomas e incapacidade neurológica. Nos pacientes recorrentes remitentes observamos sonolência excessiva diurna, fadiga e depressão ( $p = 0,001$ ). Nas formas progressivas não foi possível observar associação entre fadiga, sonolência excessiva diurna, depressão e incapacidade. **Conclusão:** Na forma remitente recorrente existe uma relação entre incapacidade funcional, sonolência excessiva diurna e fadiga, entretanto, não notamos esta associação nas formas secundariamente progressiva e primariamente progressiva.

**Palavras-chave:** esclerose múltipla; pessoas com deficiência, fadiga; distúrbios do sono por sonolência excessiva.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system marked by multiple exacerbations and remissions. It is considered an autoimmune disease with a varying course and uncertain prognosis<sup>1</sup>. Fatigue is a common and disabling symptom of MS. Some MS investigators have defined MS fatigue as a feeling of physical tiredness and lack of energy<sup>1</sup>, distinct from sadness or weakness<sup>2,3</sup>. Others have described it as extreme tiredness and the need to rest. The causes and mechanisms of fatigue in

MS remain poorly understood, and are likely to be multifactorial<sup>3</sup>. Physiological fatigue has been demonstrated in MS and seems to be central in origin, muscular dysfunction has also been reported and may result from inactivity. However, there is no correlation between the degree of physiological fatigue, and the amount of fatigue<sup>4</sup>.

Sleep disorders are frequent in patients with multiple sclerosis, interferes with daytime wakefulness, affects daily functional performance<sup>5</sup>, usually their disorders are associated

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**Conflict of interest:** There is no conflict of interest to declare.

Received 11 September 2015; Received in final form 31 January 2016; Accepted 28 March 2016.



with psychological or motor symptoms<sup>6</sup>, disease duration, clinical presentation and disruption of the sleep cycle<sup>4</sup>, and may cause marked fatigue<sup>7</sup>.

Fatigue is a common complaint in multiple sclerosis, and impairs quality of life<sup>7,8</sup>. Its pathophysiology is not fully understood, but it seems to be influenced by different factors<sup>1</sup>. Patients often describe fatigue as the most disabling symptom even when compared to weakness or spasticity<sup>3</sup>. Fatigue is usually induced by excessive physical activity and relieved by rest<sup>2,9</sup>.

Fatigue is often mistaken for excessive daytime sleepiness (EDS). However, EDS is defined as a decrease in physical and/or mental work capacity with incomplete relief at rest. Even though these are distinct clinical symptoms<sup>1,8</sup>, they frequently coexist in the same patient and may be associated with sleep disorders<sup>10</sup>.

Some studies have tried to correlate fatigue and EDS in patients with MS<sup>4</sup>, but it is difficult to differentiate between them since both may be related to sleep disorders and may occur concomitantly<sup>11,12</sup>.

The objective of this study is to assess the correlation between fatigue, excessive daytime sleepiness and the degree of disability in patients with MS.

## METHOD

We conducted a retrospective analysis of the medical records of patients with MS followed up at the neuroimmunology clinic over the period 2006-2008. The study was approved by the University's Research Ethics Committee.

All selected medical records met the following inclusion criteria: male or female patients aged 20-71, with relapsing-remitting or progressive multiple sclerosis based on McDonald's 2001 and 2005<sup>13</sup> diagnostic criteria, neurological disability measured by EDSS (Expanded Disability Status Scale) score up to 7.0<sup>14</sup>, with fatigue and sleep complaints assessed by fatigue scales and sleep disorders assessment questionnaires. In addition, patients should have been under clinical follow up for at least one year and treated with any disease modifying drugs. Incomplete medical records, records from patients suffering from acute demyelinating encephalomyelitis (ADEM) or neuromyelitis optica (NMO), and from patients with multiple sclerosis and other concurrent conditions, such as hypertension, diabetes mellitus, hypothyroidism or orthopedic, cardiac or rheumatic disorders that might cause sleep disturbances or result in neurological disability and fatigue were excluded from the study.

The presence of fatigue was assessed using the Fatigue Severity Scale (FSS): the scale includes nine (9) items, and the scores range from 1 (absence of fatigue) to 7 (fatigue present), a minimum of 28 points suggests the presence of fatigue and higher scores indicate more severe symptoms<sup>15,16</sup>.

Depression was assessed using the Beck's depression inventory, a self-administered questionnaire where higher scores indicate more severe depression<sup>17</sup>. EDS was assessed using the Epworth scale, consisting of questions about the possibility of dozing off in eight different situations; scores equal to or higher than 10 indicate excessive daytime sleepiness<sup>18</sup>.

Medical records from 912 patients were reviewed. From these, 122 have met the inclusion criteria: 82 (67%) patients had relapsing-remitting multiple sclerosis (RRMS), 15 (12%) had primary progressive disease (PPMS) and 25 (21%) had secondary progressive multiple sclerosis (SPMS) (Figure).

Statistical analysis was performed. The Student's t-test, the Pearson's chi-square test, and the Spearman correlation were used to analyze the different clinical forms, namely relapsing remitting multiple sclerosis, primary progressive multiple sclerosis, and secondary progressive multiple sclerosis, comparing the following variables: age, excessive daytime sleepiness, level of disability, depression and fatigue. The significance level admitted was  $p < 0.05$ .

## RESULTS

The patients' clinical characteristics are summarized in Table 1. Fatigue was present in 51 (64%) patients with RRMS, 14 (93%) patients with SPMS, and 19 (66%) patients with PPMS. Patients with RRMS and SPMS who experienced fatigue also complained of moderate to severe depression and we observed a correlation between fatigue and depression,  $r = 0.417$  and  $0.638$ , respectively. However, such correlation was not found in patients with PPMS. Among RRMS patients who reported fatigue, 80% ( $n = 41$ ) had an EDSS score lower than 6, on the other hand, patients with PPMS and SPMS who reported fatigue had EDSS scores higher than 6 (Table 2).

Excessive daytime sleepiness was present in 36.1% (44) of the study patients, with the following distribution: 54% of the RRMS patients ( $n = 24$ ), 15% of the PPMS patients ( $n = 7$ ), and 29% of the SPMS patients ( $n = 13$ ).

In RRMS patients ( $n = 24$ ) who complained of excessive daytime sleepiness, we noticed that EDS was associated with fatigue in 19 patients (79.1%), while 5 patients (21%) did not reach a score in the fatigue scale to receive such diagnosis, despite experiencing somnolence. Also, we observed that 18 out of these 19 patients with fatigue and EDS had lower neurological disability with an EDSS score ranging from 0 to 4 ( $p = 0.047$ ) (Table 3). Among patients with RRMS who experienced sleepiness and fatigue, we found that 63.1% (12) suffered from moderate to severe depression ( $p = 0.001$ ) and 36.8% (7) had no mood changes (Table 3).

Even though fatigue, excessive daytime sleepiness, depression, and disability were present in patients with progressive forms of multiple sclerosis, we did not find any correlation among them.

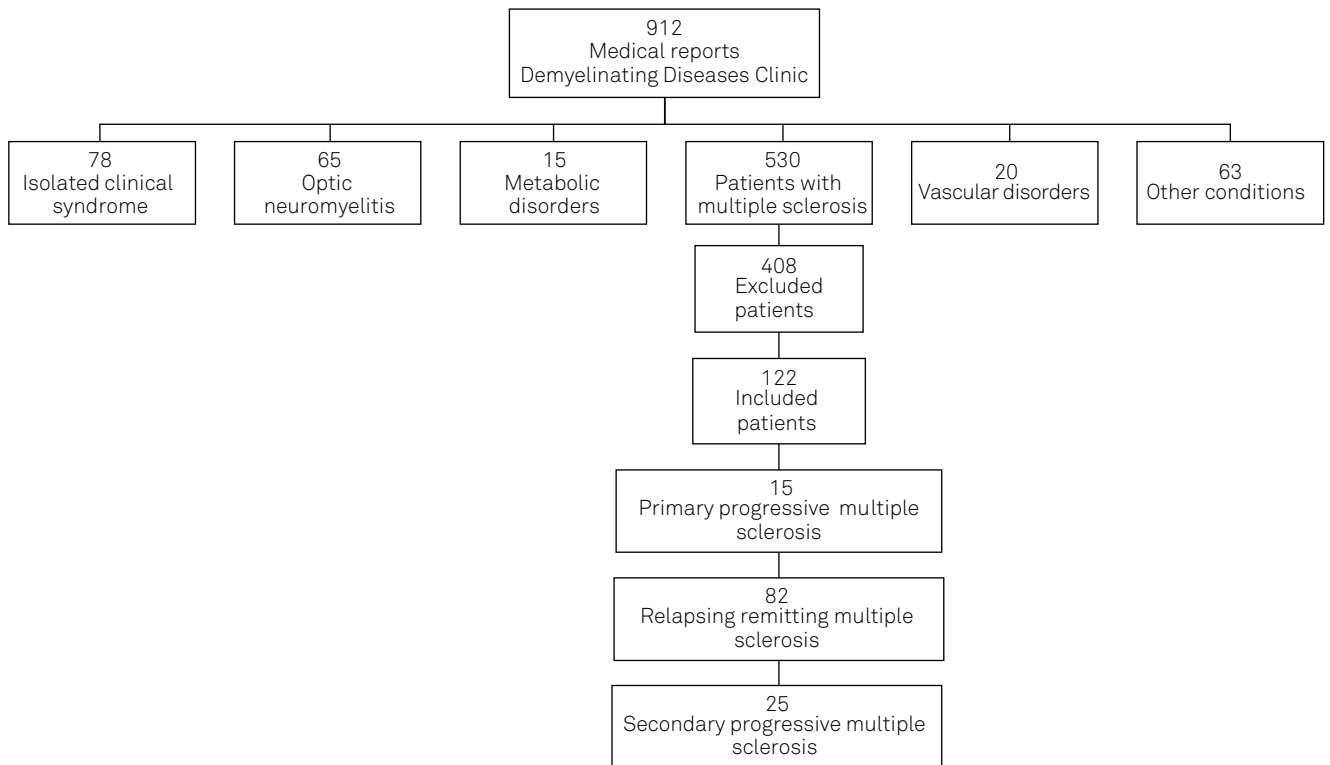


Figure. Flowchart of selected medical records.

Table 1. Patient demographics and disease characteristics.

	N	%	Median	25%	75%
Gender					
Male	41	33.6	-	-	-
Female	81	66.4	-	-	-
EDSS					
< 6 (0–5,5)	80	65.6	-	-	-
> = 6 (6–7)	42	34.4	-	-	-
Clinical forms					
RRMS	82	67.2	-	-	-
PPMS	15	12.3	-	-	-
SPMS	25	20.5	-	-	-
FSS - Fatigue					
No	38	31.1	-	-	-
Yes	84	68.9	-	-	-
EDS - Sleepiness					
No	78	63.9	-	-	-
Yes	44	36.1	-	-	-
Beck - Depression					
No	32	26.2	-	-	-
Yes	90	73.8	-	-	-
Age, yrs.			44	33	51
FSS	-	-	41	24	57
EDSS	-	-	3.5	1.5	6.0
BECK	-	-	10	7	18
EDS	-	-	7	4	11

EDSS: expanded disability status scale; RRMS: remitting recurrent multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; FSS: fatigue severity scale; EDS: excessive daytime sleepiness; Beck: Beck's depression inventory.

**Table 2.** Correlation between fatigue, disability and depression using the corresponding assessment questionnaire.

	FSS	EDSS (> = 6)	BECK
<b>RRMS</b>			
r	-	0.208	0.417*
p	-	0.060	0.001**
N (82)	51	10	15
<b>PPMS</b>			
r	-	0.369	0.463
p	-	0.176	0.082
N (15)	14	11	5
<b>SPMS</b>			
r	-	0.394	0.638*
p	-	0.051	0.001**
N (25)	19	10	13

FSS: fatigue severity scale; EDSS (> = 6): expanded disability status scale; Beck: Beck's depression inventory; RRMS: remitting recurrent multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; \*r < 0.01 statistically significant for Spearman coefficient; \*\*p < 0.05 considered as statistically significant.

## DISCUSSION

Fatigue is a symptom frequently reported by patients with MS. It is a subjective complaint, thus imposing challenges to its proper evaluation. In this study, as expected we observed that fatigue was present in all clinical forms but in RRMS it was not correlated with greater neurological disability, measured by the EDSS. On the other hand, patients with progressive forms and fatigue complaints had EDSS higher than 6. Interestingly, some authors suggested<sup>15,19,20</sup> that the motor impairment observed in MS patients might impact their functioning, requiring excessive effort to carry out their activities; such hypothesis could explain our results.

Also, it is important to highlight that depression and fatigue were present in a smaller percentage of patients in this sample (RRMS and SPMS) and, in general, both may be present in patients with reduced mobility<sup>5,21</sup>. The reduction of daily activities caused by physical limitations can cause depression, but, in our sample we were not able to determine which symptom came first<sup>5,21</sup>.

Fatigue may be linked to age and has been correlated to cognitive impairment as well<sup>6</sup>. In daily practice, we mainly use scales that predominantly assess motor functions. The EDSS scale is not appropriate for assessing cognitive dysfunction, and perhaps this could have explained why we did not find a correlation between fatigue and the EDSS score in progressive forms of the disease, where cognitive impairment is more frequent<sup>22,23</sup>. Also, we did not find an impact of age on the fatigue complaints among patients with multiple sclerosis of any type.

Excessive daytime sleepiness was present in all clinical forms and it was associated to fatigue<sup>10</sup> in approximately 25% of the patients with relapsing-remitting MS. In these patients, we were able to demonstrate that excessive sleepiness was also associated with neurological disability. Of note,

**Table 3.** Patients with fatigue and excessive daytime sleepiness.

	RRMS		PPMS		SPMS		p	Chi-Square
	Fatigue and sleepiness N (%)	Fatigue and no sleepiness N (%)	Fatigue and sleepiness N (%)	Fatigue and no sleepiness N (%)	Fatigue and sleepiness N (%)	Fatigue and no sleepiness N (%)		
Gender								
Female	7(21.9)	9(47.4)	3(42.9)	12(63.2)	5(55.6)	4(40.0)	0.577	0.488
Male	25(78.1)	10(52.6)	4(57.1)	2(28.6)	4(44.4)	6(60.0)	0.361	0.782
Beck								
No depression	29(90.6)	7(36.8)	3(42.9)	6(85.7)	5(55.6)	4(40.0)	0.001*	0.498
Depression	3(9.4)	12(63.2)	4(57.1)	1(14.3)	4(44.4)	6(60.0)	0.002*	0.778
EDSS								
< 6	23(71.9)	18(94.7)	2(28.6)	1(14.3)	4(44.4)	2(20.0)	0.047*	0.252
> = 6	9(28.1)	1(5.3)	5(71.4)	6(85.7)	5(55.6)	8(80.0)	0.003*	0.598

RRMS: remitting recurrent multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; Beck: Beck's depression inventory; EDSS: expanded disability status scale; \*p < 0.05 considered statistically significant.

we observed that in this group of patients, the lower the level of disability, the higher the chance of sleepiness. Interestingly, such findings were not consistent with what has been described previously<sup>11,26</sup> and might be explained by the fact that mildly disabled RRMS patients could be more active.

The differential diagnosis of EDS is initially based on the history of daytime function and on the analysis of daytime alertness in carrying out routine activities. In a second moment the sleeping habits should be analyzed and a polysomnography should be performed<sup>27</sup>. Excessive daytime sleepiness may result from different factors<sup>4</sup>, such as disruption of sleep cycles, autonomic dysfunction, and psychiatric disorders<sup>8</sup>; these may favor the onset of EDS and fatigue due to a non-restful sleep<sup>12,29</sup>. Patients complaining of depression quite often report difficulty in falling asleep, frequent nighttime awakenings, and early morning waking followed by fatigue throughout the day. By using validated subjective scales to measure the degree of daytime alertness, which has been proven to be effective in the diagnosis of EDS<sup>18</sup>, alongside depression and fatigue questionnaires, we were able to demonstrate a correlation between depression, disability, sleepiness, and fatigue, and confirmed the notion that these symptoms are frequently concurrent.

Recent studies suggest an association between fatigue and abnormal sleep cycles or interrupted sleep and interference with the circadian rhythm; however, in this population we could not address these factors, since we did not assess sleep cycles or performed polysomnographic studies<sup>5,12,26,29</sup>. Usually, most of the studies describe patients with MS divided into subgroups: with and without fatigue, regardless the clinical presentation<sup>12,30</sup>, therefore reports on the progressive

forms are limited. Our study took an alternative approach, by analyzing the frequency of fatigue and EDS in different clinical forms of the disease. In this way, we may have missed the comparison between fatigued and non-fatigued patients, but we added an important piece of information about the different clinical forms of the disease.

Although it has been demonstrated that cognitive impairment is related to fatigue, we acknowledge one important limitation of this work which is the lack of neuropsychology evaluation. The neuropsychology battery tests can only be performed by trained neuropsychologists and during the period this study was performed, we did not have such specialist available. Therefore, the lack of correlation between fatigue and EDSS in the progressive forms may reflect such limitation.

The association between sleepiness and fatigue further supports the assumption that both are present in MS patients, while showing distinct and unique characteristics according MS subtypes. When seeing patients with these symptoms, healthcare professionals should establish a definite diagnosis based on the medical history and on the use of specific scales to guide the therapeutic approach, since it is possible that initially by treating fatigue and depression, one can alleviate or eliminate the symptoms of EDS.

In conclusion, fatigue and excessive daytime sleepiness are frequent in patients with MS. There was a positive correlation between functional disability, excessive daytime sleepiness, and fatigue in remitting MS and no association between the degree of disability and fatigue in patients with progressive subtypes. Also, we noted an association of fatigue and depression in RRMS and SPMS patients.

## References

1. Strober LB, Arnett PA. An examination of four models predicting fatigue in multiple sclerosis. *Arch Clin Neuropsychol*. 2005;20(5):631-46. doi:10.1016/j.acn.2005.04.002
2. Zifko UA. Management fatigue in patients with multiple sclerosis. *Drugs*. 2004;64(12):1295-304. doi:10.2165/00003495-200464120-00003
3. Schreurs KM, Ridder DT, Bensing JM. Fatigue in multiple sclerosis: reciprocal relationships with physical disabilities and depression. *J Psychosom Res*. 2002;53(3):775-81. doi:10.1016/S0022-3999(02)00326-4
4. Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. *Mult Scler*. 2006;12(4):481-6. doi:10.1191/135248506ms1320oa
5. Alarcia R, Ara JR, Martín J, López A, Bestué M, Bertol V et al. [Sleep disorders in multiple sclerosis]. *Neurología*. 2004;19(10):704-9. Spanish.
6. Fleming WE, Pollak CP. Sleep disorders in multiple sclerosis. *Semin Neurol*. 2005;25(1):64-8. doi:10.1055/s-2005-867075
7. Bøe Lunde HM, Aae TF, Indrevåg W, Aarseth J, Bjorvatn B, Myhr KM et al. Poor sleep in patients with multiple sclerosis. *PLoS One*. 2012;7(11):e49996. doi:10.1371/journal.pone.0049996
8. Attarian HP, Brown KM, Duntley SP, Carter JD, Cross AH. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Arch Neurol*. 2004;61(4):525-8. doi:10.1001/archneur.61.4.525
9. Leavitt VM, DeLuca J. Central fatigue: issues related to cognition, mood and behavior, and psychiatric diagnoses. *PM R*. 2010;2(5):332-7. doi:10.1016/j.pmrj.2010.03.027
10. Labuz-Roszak B, Kubicka-Bączyk K, Pierzchała K, Machowska-Majchrzak A, Skrzypek M. Fatigue and its association with sleep disorders, depressive symptoms and anxiety in patients with multiple sclerosis. *Neurol Neurochir Pol*. 2012;46(4):309-17. doi:10.5114/ninp.2012.30261
11. Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. *Mult Scler*. 2008;14(8):1127-30. doi:10.1177/1352458508092807
12. Braley TJ, Chervin RD, Segal BM. Fatigue, tiredness, lack of energy, and sleepiness in multiple sclerosis patients referred for clinical polysomnography. *Mult Scler Int*. 2012;2012:ID673936. doi:10.1155/2012/673936
13. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiplesclerosis. *Ann Neurol*. 2001;50(1):121-7. doi:10.1002/ana.1032
14. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-52. doi:10.1212/WNL.33.11.1444

15. Mendes MF, Tilbery HP, Balsimell S, Felipe E, Moreira MA, Barão-Cruz AM. Fadiga na forma renitente recorrente da esclerose múltipla. *Arq Neuropsiquiatr*. 2000;58(2B):471-5. doi:10.1590/S0004-282X2000000300012
16. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg A D. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46(10):1121-3.
17. Gorenstein C, Andrade L. Inventário de Depressão de Beck: propriedades psicométricas da versão em português. *Rev Psiq Clín*. 1998;25(5):245-50.
18. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14:540-5. doi:10.1378/chest.103.1.30
19. Calabrese M, Rinaldi F, Grossi P, Mattisi I, Bernardi V, Favaretto A et al. Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing-remitting multiple sclerosis. *Mult Scler*. 2010;16(10):1220-8. doi:10.1177/1352458510376405
20. Kaynak H, Altıntaş A, Kaynak D, Uyanik O, Saip S, Ağaoğlu J et al. Fatigue and sleep disturbance in multiple sclerosis. *Eur J Neurol*. 2006;13(2):1333-9. doi: 10.1111/j.1468-1331.2006.01499.x
21. Achiron A, Chapman J, Magalashvili D, Dolev M, Lavie M, Bercovich E et al. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. *PLoS One*. 2013;8(8):e71058. doi:10.1371/journal.pone.0071058
22. Papatthanasiou A, Messinis L, Georgiou VL, Papatthanopoulos P. Cognitive impairment in relapsing remitting and secondary progressive multiple sclerosis patients: efficacy of a computerized cognitive screening battery. *ISRN Neurol*. 2014;2014:ID151379. doi:10.1155/2014/151379
23. Merkelbach S, Schulz H, Kölmel HW, Gora G, Klingelhöfer J, Dachsel R et al. Fatigue, sleepiness, and physical activity in patients with multiple sclerosis. *J Neurol*. 2011;258(1):74-9. doi:10.1007/s00415-010-5684-3
24. Mills RJ, Young CA. The relationship between fatigue and other clinical features of multiple sclerosis. *Mult Scler*. 2011;17(5):604-12. doi:10.1177/1352458510392262
25. Lobentanz IS, Asenbaum S, Vass K, Sauter C, Klösch G, Kollegger H et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand*. 2004;110(1):6-13. doi:10.1111/j.1600-0404.2004.00257.x
26. Pokryszko-Dragan A, Bilińska M, Gruszka E, Biel Ł, Kamińska K, Konieczna K. Sleep disturbances in patients with multiple sclerosis. *Neurol Sci*. 2013;34(8):1291-6. doi:10.1007/s10072-012-1229-0
27. Giorelli AS, Santos PP, Carnaval T, Gomes MM. Sonolência excessiva diurna: aspectos clínicos, diagnósticos e terapêuticos. *Rev Bras Neurol*. 2012;48(3):17-24.
28. McWhirter D, Bae C, Budur K. The assessment, diagnosis, and treatment of excessive sleepiness: practical considerations for the psychiatrist. *Psychiatry (Edgmont)*. 2007;4(9):26-35.
29. Mohr DC, Hart SL, Goldberg A. Effects of treatment for depression on fatigue in multiple sclerosis. *Psychosom Med*. 2003;65(4):542-47. Doi:10.1097/01.PSY.000007475711682.96
30. Ghajarzadeh M, Sahraian MA, Fateh R, Daneshmand A. Fatigue, depression and sleep disturbances in Iranian patients with multiple sclerosis. *Acta Med Iran*. 2012;50(4):244-9.