

ARTIGO ORIGINAL/ORIGINAL ARTICLE

IMPRESS: Impact of Baseline Depression in Multiple Sclerosis Patients Starting Treatment with Interferon β -1a**IMPRESS: Impacto da Depressão de Base em Doentes com Esclerose Múltipla que Iniciaram Tratamento com Interferão β -1a**

 António Salgado ¹,  Ângela Silva ²,  Ernestina Santos ³,  Catarina Flores ^{4,*},  Rita Lau ⁴

1-Neurology Department / Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal

2-Neurology Department / Hospital Da Senhora Da Oliveira, Guimarães, Portugal

3-Neurology Department / Centro Hospitalar Universitário do Porto - Hospital de Santo António, Porto, Portugal

4-Medical Department / Biogen Portugal, Lisboa, Portugal

DOI: <https://doi.org/10.46531/sinapse/AO/230009/2023>

Abstract

Introduction: Some studies suggest an association between interferon beta (IFN β) therapies and the development of depression symptoms in multiple sclerosis (MS). This study aimed to evaluate the impact of baseline depression (BLD) on depression score variation at 24 months (m) in MS patients starting treatment with IFN β -1a.

Methods: Multicenter, prospective, observational study in patients recently diagnosed with relapsing-remitting MS or clinically isolated syndrome, starting treatment with IFN β -1a intramuscular. The physician and the patient completed a questionnaire in each visit (baseline, 6, 12, 18 and 24 m) including demographic and clinical data, disability, depression, fatigue, balance, mental state, sleepiness and coping, compliance with MS treatment, treatment discontinuation, and adverse events.

Results: A total of 110 patients were included in the analysis, 20% with BLD. Both patient groups (with and without BLD) were similarly distributed concerning baseline demographic and clinical characteristics, except for EDSS, that was higher in patients with BLD (median EDSS of 1.25 \pm 1.75 vs 1.0 \pm 1.5; $p=0.047$). In BLD patients, only depression severity varied significantly over the five evaluations ($p=0.034$), with a marked decrease at 6 months. In patients without BLD, no significant variations were observed. BLD had a significant effect on variation in depression severity at 24 m ($p=0.0253$) and baseline fatigue was a good predictor for global fatigue over the study period ($p=0.0399$).

Conclusion: Despite its impact on MS patients, depression is frequently underdiagnosed and undertreated. IMPRESS results suggest that BLD and fatigue scores in MS patients influence score variations over the treatment period. Further research on depression and MS association may lead to better understanding of this relation.

Resumo

Introdução: Alguns estudos sugerem uma associação entre as terapias com interferão beta (IFN β) e o desenvolvimento de sintomas de depressão na esclerose múltipla (EM). Este estudo teve como objetivo avaliar o impacto da depressão basal (DB) na variação do score de depressão aos 24 meses (m) em doentes com EM a iniciar tratamento com IFN β -1a.

Métodos: Estudo observacional, prospetivo, multicêntrico em doentes com diag-

Informações/Informations:

Artigo Original, publicado em Sinapse, Volume 23, Número 3, julho-setembro 2023. Versão eletrónica em www.sinapse.pt; Original Article, published in Sinapse, Volume 23, Number 3, July-September 2023. Electronic version in www.sinapse.pt

© Autor (es) (ou seu (s) empregador (es)) e Sinapse 2023. Reutilização permitida de acordo com CC BY-NC. Nenhuma reutilização comercial. © Author(s) (or their employer(s)) and Sinapse 2023. Re-use permitted under CC BY-NC. No commercial re-use.

Keywords:

Depression/etiology; Interferon beta-1a; Multiple Sclerosis/ complications; Multiple Sclerosis/drug therapy.

Palavras-chave:

Esclerose Múltipla/ complicações; Esclerose Múltipla/tratamento farmacológico; Interferão beta-1a.

Autor Correspondente /*Corresponding Author:**

Catarina Flores
Biogen Portugal
Av. Duque de Ávila, 141 -
7.º andar
1050-081 Lisboa, Portugal
catarina.flores@biogen.com

Recebido / Received: 2023-02-03

Aceite / Accepted: 2023-10-03

Publicado / Published: 2023-10-18

nóstico recente de EM surto-remissão ou síndrome clinicamente isolada, a iniciar tratamento com IFN β -1a por via intramuscular. O médico e o doente completaram um questionário em cada visita (*baseline*, 6, 12, 18 e 24 m), incluindo dados demográficos e clínicos, incapacidade, depressão, fadiga, equilíbrio, estado mental, sonolência e *coping*, adesão ao tratamento de EM, descontinuação do tratamento e eventos adversos.

Resultados: Foram incluídos 110 doentes na análise, 20% com DB. Os grupos de doentes (com e sem DB) foram distribuídos de forma semelhante relativamente a características demográficas e clínicas basais, exceto na EDSS, que foi mais elevada em doentes com DB (EDSS mediana de $1,25 \pm 1,75$ vs $1,0 \pm 1,5$; $p = 0,047$). Em doentes com DB, apenas a gravidade da depressão variou significativamente ao longo das cinco avaliações ($p = 0,034$), com uma diminuição acentuada aos 6 meses. Em doentes sem DB, não foram observadas variações significativas. A DB teve um efeito significativo na variação da gravidade da depressão aos 24 m ($p = 0,0253$) e a fadiga basal foi um bom preditor para a fadiga global durante o período de estudo ($p = 0,0399$).

Conclusão: Apesar do seu impacto nos doentes com EM, a depressão é frequentemente subdiagnosticada e subtratada. Os resultados do IMPRESS sugerem que os scores de depressão e fadiga basais em doentes com EM influenciam as variações dos scores durante o período de tratamento. Estudos adicionais sobre a associação entre depressão e EM podem levar a uma melhor compreensão sobre esta relação.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and degenerative disease of the central nervous system (CNS).¹ The clinical manifestations of MS include several signs and symptoms of neurological dysfunction. In the advanced stages of the disease, MS leads to disability, which has a devastating effect on patients, both from medical, social and financial standpoints.²⁻⁵

Depression has a markedly negative impact on quality of life (QoL) and cognitive function, accounting for a large number of lost working days.⁶ In this sense, depression is considered one of the most common and incapacitating diseases of this century.⁷ Despite being the most common psychiatric disorder in MS patients, depression remains largely underdiagnosed and undertreated.⁸ The presence of depression symptoms has been reported in all stages of MS, including the early stages of the disease, where 14% of patients are thought to be affected.⁶ Moreover, depression appears to be more prevalent in women and patients under 45 years of age.⁹

In a recent review, the percentage of MS patients experiencing depression symptoms ranged between 4.3%¹⁰ and 59.6%.⁹ This variability may be due to differences in sample size, clinical measures and evaluation

methods (namely diagnostic criteria) between the studies reviewed. Additionally, the risk of major depressive disorder (MDD) in these patients begins with the first symptoms of MS^{11,12} and persists over their lifetime, with a prevalence of 19%-54%.^{6,13,14} In MS patients, the risk of developing MDD over their lifetime is higher than that reported for other chronic diseases, including other disabling neurological disorders.^{6,15}

In addition to representing a key factor in determining QoL in MS patients,¹⁶ depression may lead to suicidal behaviours¹⁷ (a suicide risk of 15% has been reported in these patients⁶) and affect treatment compliance in patients receiving disease-modifying drugs.^{18,19} Therefore, the ability to identify depression symptoms in clinical practice plays an essential role in improving outcomes in MS patients, as these symptoms are potentially treatable.²⁰

The causes of depression in MS patients are still widely unknown. Numerous factors are thought to be involved. It has been suggested that the changes in brain structure associated with MS, as well as immuno-inflammatory, genetic and psychosocial factors, may play a role in the development of depression in MS patients.^{20,21} However, more evidence is required to support these hypotheses.

In addition to depression, about 65% experience clinically significant fatigue.²² These symptoms have been

demonstrated to be correlated and effective treatment of depression helps relieve fatigue.²³ This is considered a very relevant finding, since fatigue is one of the most disabling symptoms of MS and one of the major causes of lost working days in MS patients.²⁴

The negative impact of depression on cognitive function in MS patients has also been widely demonstrated. Cognitive impairment has been reported in 45%-65% of patients.²⁰ Cognitive performance, namely working memory and data processing speed, is significantly impaired in patients with MS and depression.²⁰

Several treatment options based on interferon beta (IFN β) have been used in MS patients over the last 20 years. Some studies suggest the existence of an association between IFN β therapies and the development of depression symptoms²⁵; however, this association has not been confirmed.

The results of studies on depression in MS and the underlying mechanisms have been difficult to interpret, owing to the different characteristics of study populations, in terms of disability scores, disease severity, age, gender and treatment regimens.^{6,12,15} In this sense, a study in a homogenous, well-characterized patient population starting a specific treatment regimen might help clarify and understand the association between depression and MS.

The primary goal of this study was to evaluate the impact of baseline depression on depression score variation at 24 months (m) in recently diagnosed MS patients starting treatment with IFN β -1a intramuscular (IM). Secondary endpoints included the evaluation of the impact of baseline fatigue on fatigue score variation at 24 m and the effect of sleep disorders and treatment compliance on depression outcomes. Exploratory evaluations included balance, mental state and coping strategies.

Material and Methods

IMPRESS was a multicenter, prospective, observational study in patients recently diagnosed with relapsing-remitting MS (RRMS) or clinically isolated syndrome (CIS) starting treatment with IFN β -1a IM. Patients were recruited consecutively over 24 m at the Neurology Services of 13 Healthcare Centers in Portugal. All Centers' Ethic Committees gave their approval for study implementation and patients gave their informed consent prior to any study procedure.

Patient eligibility was determined according to the

following inclusion criteria: diagnosis of RRMS or CIS according to the 2010 MacDonald revised criteria; age \geq 18 years; indication for starting treatment with IFN β -1a IM, according to the indications approved by the European Medicines Agency (EMA); expanded disability status scale (EDSS) score \leq 3.0; and provision of informed consent. Initially, patients should also be MS treatment-naïve; however, in the course of the study, prior MS treatments other than immunomodulators were allowed in order to achieve a minimum required sample. All patients failing to meet pre-defined inclusion criteria or presenting with neurological, psychiatric or rheumatologic comorbidities were excluded from the study.

Patients were evaluated in five visits: first visit (baseline) and at 6, 12, 18 and 24 m. Both the physician and the patient completed a questionnaire in each visit. The following data were collected: demographic and clinical data (MS characteristics; concomitant medication) (first visit); flu-like syndrome (6 m); relapses, laboratory test results (hemoglobin levels and thyroid/renal/liver function), disability, depression, fatigue, balance, mental state, sleepiness and coping (first visit – baseline – and 6, 12, 18 and 24 m visits). Compliance with MS treatment, as well as treatment discontinuation, reasons for discontinuation, adverse events (AEs) and treatment changes were also evaluated.

Disability was evaluated based on EDSS scores. Depression severity was evaluated based on the Beck Depression Inventory II (BDI-II), a standardized 21-item self-administered questionnaire used to assess the presence of depression symptoms over the last two weeks.²⁶ Scores range from 0 to 63, depending on depression severity: 0-13 minimal depression; 14-19 mild depression; 20-28 moderate depression; and 29-63 severe depression. The Portuguese version of this inventory has been validated by the Mapi Institute.²⁷ Regarding secondary endpoints, fatigue was evaluated based on the Fatigue Scale for Motor and Cognitive Functions (FSMC). Sleep disorders were evaluated based on the Epworth sleepiness scale²⁸; balance was evaluated based on the Fullerton Advanced Balance Scale (FAB). These two scales were translated into Portuguese and adapted to the Portuguese culture prior to study conduction. Mental state was evaluated based on the Mini Mental State Examination (MMSE); coping strategies were evaluated based on the Brief Cope scale, whose Portuguese versions have already been validated.^{29,30}

According to BDI-II baseline scores, patients were considered as having baseline depression or without baseline depression. Per protocol, the distribution ratio for baseline depression (absence/presence of baseline depression) should be 2:1.

Statistical analysis

The R I v3.4.0 software was used to conduct statistical analysis. Descriptive analysis of continuous variables involved the estimation of the mean, median, quartiles, minimum and maximum values, and standard deviation; absolute and relative frequencies were determined for categorical values.

Regarding categorical values, Pearson's chi-square test was used to test differences between groups for statistical significance. Alternatively, Fisher's exact test was used when the expected absolute frequencies were lower than 5. Student's t-test was used to test differences between groups for statistical significance for normally distributed variables; the Wilcoxon test was used for continuous variables that did not follow a normal distribution. The Shapiro-Wilk test was used to test continuous variables for normality. All statistical tests were performed at a significance level of 95%.

Results

A total of 119 patients with RRMS or CIS were recruited consecutively between April 2011 and June 2015. The percentage of patients who refused enrolment was <5%. Five patients were excluded for failing to complete the BDI-II questionnaire in the first visit; a further 4 patients with EDSS scores >3 were also excluded. Therefore, data were only available for 110 patients. Of the 110 patients with available data, 64% (n=70) completed all five study evaluations, whereas 14% (n=15) only completed the first evaluation. Most patients in the analysis population did not experience baseline depression (80%; n=88); 20% of patients presented with baseline depression (n=22).

First evaluation

Both patient groups (with and without baseline depression) were similarly distributed in terms of age, gender and academic qualifications. However, the two groups were less homogeneous in terms of occupation (**Table 1**).

Approximately three quarters (n=81; 74%) of the patients included in the analysis population had RRMS; only 24% (n=26) had CIS (**Table 2**). The percentage of patients with RRMS and CIS, duration of the disease, age at diagnosis, age upon appearance of the first symp-

Table 1. Demographic characteristics of the study population.

	Total (n=110)	With depression (n=22)	Without depression (n=88)
Age – years (mean ± SD)	36.39 ± 8.64	38.86 ± 9.31	35.76 ± 8.41
Gender – n (%)			
Male	34 (30.91)	5 (22.73)	29 (32.95)
Female	76 (69.09)	17 (77.27)	59 (67.05)
Academic qualifications – n (%)			
1-4 years	7 (6.36)	3 (14.29)	4 (4.76)
5-12 years	54 (49.09)	12 (57.14)	42 (50)
Secondary education (completed)	3 (2.73)	1 (4.76)	2 (2.38)
University degree	38 (34.55)	5 (23.81)	33 (39.29)
Master's degree	3 (2.73)	0 (0)	3 (3.57)
Occupation – n (%)			
Unemployed	8 (7.27)	2 (9.09)	6 (6.90)
Homemaker	3 (2.73)	3 (13.64)	0 (0)
Employed	88 (80.00)	15 (68.18)	73 (83.91)
Student	8 (7.27)	1 (4.55)	7 (8.05)
Retired	2 (1.82)	1 (4.55)	1 (1.15)

SD, standard deviation

Table 2. MS characteristics.

	With depression (n=22)	Without depression (n=88)	<i>p</i>
Type – n (%)			
RRMS	16 (76.19)	65 (75.58)	1.000
CIS	5 (23.81)	21 (24.42)	
Duration of the disease(*) – n (%)			0.651
<1 week	0 (0)	1 (1.15)	
1-26 weeks	6 (27.27)	22 (25.29)	
6-12 months	4 (18.18)	6 (6.90)	
1-2 years	2 (9.09)	18 (20.69)	
2-5 years	5 (22.73)	23 (26.44)	
5-10 years	3 (13.64)	10 (11.49)	
>10 years	2 (9.09)	7 (8.05)	
Age at diagnosis – mean ± SD	38.56 ± 9.11	34.55 ± 8.68	0.104
Age at 1 st symptoms – mean ± SD	35.55 ± 9.84	32.43 ± 9.44	0.190
Time between 1 st symptoms and diagnosis – n (%)			
<1 week	3 (16.67)	6 (8.11)	0.963
1-26 weeks	4 (22.22)	17 (22.97)	
6-12 months	1 (5.56)	5 (6.76)	
1-2 years	3 (16.67)	14 (18.92)	
2-5 years	5 (27.78)	20 (27.03)	
5-10 years	1 (5.56)	7 (9.46)	
>10 years	1 (5.56)	5 (6.76)	
Time to diagnosis – baseline – n (%)			
<1 week	0 (0)	2 (2.86)	0.039
1-26 weeks	12 (66.67)	49 (70)	
6-12 months	1 (5.56)	5 (7.14)	
1-2 years	1 (5.56)	8 (11.43)	
2-5 years	1 (5.56)	4 (5.71)	
5-10 years	3 (16.67)	0 (0)	
>10 years	0 (0)	2 (2.86)	
Relapses in the previous 12 months – n (%)	16 (72.73)	54 (61.36)	0.457
No. of relapses – median ± IQR	1 ± 1	1 ± 0	0.318
EDSS – median ± IQR	1.25 ± 1.75	1.0 ± 1.5	0.047

RRMS, relapsing remitting multiple sclerosis; CIS, clinically isolated syndrome; SD, standard deviation; IQR, interquartile range

* Time period elapsed between the appearance of the first symptoms and the date of the first study visit.

toms and time elapsed between the appearance of the first symptoms and the date of diagnosis were similar in both groups. However, the duration of the disease was longer than 5 years in 20%-25% of patients, who had been diagnosed more than 2 years before the first visit (including two patients diagnosed more than 10 years before the first visit).

The percentage of patients who experienced relapses in the 12 months prior to the first evaluation and the

number of relapses were similar in both groups, despite being slightly higher in patients with baseline depression (73% vs 61%, $p=0.457$; median of 1 ± 1 vs 1 ± 0 ; $p=0.318$, respectively). Disability was significantly higher in patients with baseline depression (median EDSS of 1.25 ± 1.75 vs 1.0 ± 1.5 ; $p=0.047$). Only 50% of patients with baseline depression had EDSS scores ≤ 1 ; 18% had EDSS scores > 2 . The number of relapses requiring treatment with corticosteroids, a visit to an emergency

service or hospitalization was similar in both groups.

Twelve patients with baseline depression, and 24 patients without baseline depression were treated with symptom relief medications at baseline, with no statistically significant difference found between both patient groups. However, only patients without baseline depression were receiving nonsteroidal anti-inflammatories (33.3% vs 0% in patients with baseline depression), and anti-depressants and medications used to manage fatigue and sleep disorders were more common in patients with baseline depression (58.3%, 25.0% and 41.7% vs 33.3%, 8.3% and 20.8% in patients without baseline depression, respectively).

Anomalous laboratory test results at baseline, namely anemia and liver insufficiency, were observed in a very small number of patients, reported in one and two patients in each group, and thyroid function changes, reported in two patients without baseline depression.

According to BDI-II scores in the first visit, most patients with baseline depression (41%) suffered from mild depression, followed by 32% with severe depression and 27% with moderate depression.

All patients presented with good mental state (MMSE ≥ 24); however, fatigue and sleepiness scores were significantly higher in patients with baseline depression. Regarding coping strategies, self-distraction, use of instrumental support, planning and acceptance scores were significantly higher in patients with baseline depression, while the opposite was found for behavioral disengagement.

Poor compliance with MS treatment due to forgetfulness was higher in patients with baseline depression (53% vs 32%; $p=0.1478$), although the difference between both patient groups was not statistically significant. No association was found between treatment compliance and variation in depression scores at 12 and 24 m.

Variation in depression scores

Variations in depression, fatigue, balance, sleepiness and mental state scores over the five evaluations performed were similar for both patient groups (with and without baseline depression). However, statistical analysis of the differences found could not be performed, owing to sample limitations (Fig. 1).

As the differences between both groups could not be statistically tested, within-group variations were analyzed. In patients with baseline depression, only depression severity varied significantly over the five study eval-

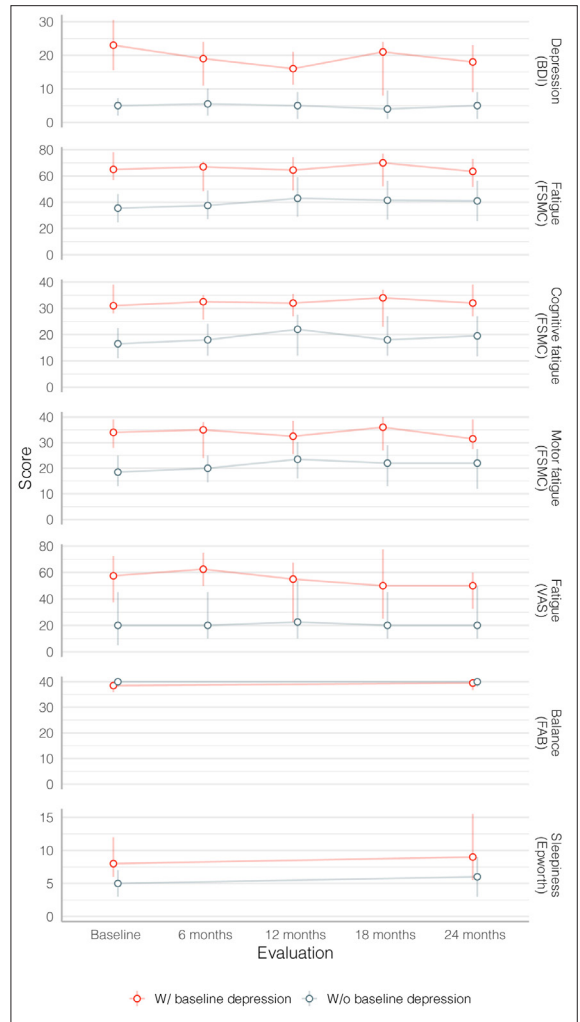


Figure 1. Variations in depression, fatigue, balance and sleepiness scores over the study period.

Note: points indicate median values; lines indicate the IQR.

uations ($p=0.034$), with a marked decrease observed as early as 6 months (Table 3).

In patients without baseline depression, no significant variations in parameters that could be statistically analyzed were observed over the five study evaluations (depression and sleepiness based on the Epworth scale; $p=0.165$ and 0.787 , respectively).

Evaluation of outcomes

Analysis of the impact of baseline parameters on depression score variation at 24 m (primary endpoint) revealed that only baseline depression had a significant effect on variation in depression severity at 24 m ($p=0.0253$). A median improvement of depression (i.e. significant decrease in BDI-II scores) was reported in patients with baseline depression, compared with patients

Table 3. Variations in depression, fatigue and sleepiness scores over the study period in patients with baseline depression.

	n	Baseline Mean ± SD	6m Mean ± SD	12m Mean ± SD	18m Mean ± SD	24m Mean ± SD	P
Depression (BDI-II)	22	23.59 ± 8.62	17.76 ± 9.30	16.21 ± 7.05	16.53 ± 9.22	17.69 ± 11.00	0.034 ^a
Fatigue (FSMC)	22	67.25 ± 14.90	62.25 ± 16.90	61.0 ± 19.9	61.2 ± 18.3	61.25 ± 17.30	0.937 ^a
Cognitive fatigue (FSMC)	22	33.00 ± 8.59	30.31 ± 7.96	30.44 ± 9.10	29.53 ± 9.79	31.08 ± 9.33	0.775 ^a
Motor fatigue (FSMC)	22	34.71 ± 6.93	32.35 ± 9.35	31.5 ± 11.2	32.75 ± 10.20	30.83 ± 10.30	0.803 ^a
Fatigue (visual analogue scale)	22	51.75 ± 28.50	56.07 ± 25.60	47.67 ± 24.00	48.67 ± 28.10	46.36 ± 24.30	0.819 ^a
Sleepiness (Epworth)	10	8.955 ± 3.850				10.30 ± 5.87	0.105 ^b

SD, standard deviation

a: Linear mixed model (for differences between measures)

b: Student's paired sample t-test

without baseline depression. On the contrary, the presence of baseline fatigue or sleepiness had no significant effect on depression score variation at 24 m.

Baseline fatigue (secondary endpoint) was a good predictor for global fatigue over the study period, both in terms of global fatigue and its cognitive and motor components ($p=0.0399$, $p=0.0493$ and $p=0.0407$, respectively). Median fatigue scores remained relatively unchanged at 24 m in patients with baseline fatigue, whereas significant increases were observed in patients without baseline fatigue.

Of the 110 patients initially included in the analysis population, 37 withdrew from the study before its completion, including 22 patients who withdrew from the study at 12 m. Study withdrawal frequency was slightly higher in patients with baseline depression, although the difference between both patient groups was not statistically significant. The most common reason for early study withdrawal was discontinuation of treatment with IFN β -1a ($n=31$), primarily due to AEs ($n=17$), lack of efficacy ($n=7$) and disease progression ($n=7$). The most commonly reported AEs were flu-like syndrome ($n=7$) and injection site reactions ($n=5$). Most of the 24 patients who started a different treatment after withdrawing from the study received dimethyl fumarate ($n=6$), glatiramer acetate ($n=5$), subcutaneous IFN β -1a ($n=4$) or Peg-IFN β -1a ($n=4$).

Discussion

Despite its impact on the QoL of MS patients, depression is frequently underdiagnosed and undertreated.^{31–33}

The goal of the IMPRESS study was to investigate variations in depression severity in MS patients treated with IFN β -1a and how this condition is influenced by baseline depression, fatigue and sleep disorders, as well

as treatment compliance.

Study results suggested that the presence or absence of baseline depression is related to variations in depression scores over the treatment period, as no significant variations in depression severity were observed in patients without baseline depression (or depression controlled with medication), whereas depression improved slightly in patients with baseline depression, even in the presence of higher EDSS. Although the extent to which this improvement may be due to the start or change of anti-depressant treatment cannot be ascertained, as the use of anti-depressants during the study period was not recorded, the measurable improvements observed as early as 6 months, which persisted up to 12 months of treatment, are suggestive of such an effect.

On average, fatigue worsened at 24 months in patients without baseline fatigue, whereas it remained unchanged over the study period in patients with baseline fatigue.

In this study, MS patients (RRMS or CIS) with baseline depression accounted for 20% of the analysis population, which falls within the wide prevalence range described in other studies (4.3%-59.6%). When diagnosing MS patients, assuming that they are likely to develop symptoms of depression, fatigue and cognitive impairment and screening these symptoms, may help ensure their timely and effective treatment.

Nevertheless, the number of studies concerning the pharmacological treatment of depression associated with MS available in the literature is very low. A review carried out in 2011³⁴ included only two randomized clinical trials, one that investigated the effect of desipramine³⁵ and the other the effect of paroxetine, both versus placebo.³⁶ Both treatments were mildly effective (differences not significant) and associated

with AEs. Other treatment options were investigated in post-treatment studies, namely tranlycypromine,³⁷ imipramine,³⁸ sertraline,³⁹ moclobemide,⁴⁰ fluoxetine⁴¹ and duloxetine,²³ which are already considered effective treatments for depression in MS patients. Nevertheless, a preferred medication cannot yet be selected for these patients, as no head-to-head trials have been conducted. A Cochrane review revealed that no sufficient evidence is available concerning the efficacy of anti-depressants in MS patients.⁴² The American Academy of Neurology (AAN) also reported that no sufficient evidence exists regarding the benefits of treatment with anti-depressants in MS patients, alerting to the need to investigate the efficacy of treatment options commonly used in other patients in this subpopulation.⁸

Although an eventual association between treatment regimens based on IFN β and the development of depression symptoms in MS patients has been investigated, results are still inconclusive. In a study conducted by Zephir *et al.*,⁴³ no association was found between treatment with IFN β and the development of depression symptoms. A meta-analysis of 6 controlled clinical trials and 17 non-controlled trials with IFN β -1a also failed to establish a relationship between this medication and suicidal behaviors or increased depression scores.⁴⁴ In the BEYOND study, a randomized clinical trial that compared the incidence of depression in patients receiving IFN β -1b or glatiramer acetate, no significant differences were found in the risk of depression between treatment groups, as evaluated based on the BDI scale.⁴⁵ The results of key clinical trials of disease-modifying drugs revealed that the incidence of self-reported depression symptoms was similar in the treatment and placebo arms in MS patients treated with IFN β -1a^{46,47} and IFN β -1b,⁴⁸ although the incidence of depression symptoms was not always reported. Besides the study limitations, the results of IMPRESS study, in MS patients treated with IFN β -1a, suggest an improvement on depression scores in patients with baseline depression, and no depression was found in those without baseline depression, over the study period.

The EPOC (Evaluate Patient Outcomes) study investigated the effect of switching treatment from an injectable medication (IFN β and glatiramer acetate) to fingolimod on depression symptoms in MS patients, as evaluated based on the BDI-II scale.⁴⁹ This study revealed that the percentage of patients with BDI-II scores

> 13 at 6 months decreased significantly, from 50.5% to 25.3%. Depression improved in RRMS patients whose treatment was switched to fingolimod, compared with patients whose treatment remained unchanged or was switched to another injectable option.

Study limitations

This study has several methodological limitations.

The patient distribution ratio for baseline depression (absence/presence of baseline depression) (4:1) was much higher than that specified in the study protocol (2:1). The small number of patients with depression (virtually half of the 40 patients initially intended) compromised the statistical power of the analyses conducted.

On the other hand, the change of the inclusion criteria which allowed the inclusion of patients who had already received treatment for MS other than immunomodulators, resulted in the inclusion of patients at later stages of the disease which could have impacted the results; in fact, over 20% of participants had been diagnosed more than 5 years before the start of the study.

Another important limitation was the lack of data on the use of anti-depressant medications over the study period. The percentage of patients taking anti-depressants at the beginning of the study was high in both groups. Moreover, no data are available on whether patients increased the dose, interrupted treatment, or initiated treatment with anti-depressants during the study period. These facts compromise the interpretation of study results and prevent reliable conclusions from being drawn, namely concerning baseline characteristics – depression, fatigue and sleepiness – and variation in depression severity over the study period, which may be masked by unknown changes in anti-depressant treatment. The improvement of depression in patients with depression at baseline could be explained because an anti-depressive treatment was started. Additionally, the IFN-therapy could also have had an effect because of MS stabilization and with association of the co-occurrence of depression, as other unconsidered effects of MS care.

Conclusion

This study suggests that baseline depression and fatigue scores in MS patients influence score variations over the treatment period. However, study results should be interpreted with caution, particularly in what concerns depression, owing to the small sample size and

uncontrolled bias possibly introduced by medication.

Study results evidence the importance of evaluating the presence of depression in MS patients, as the prevalence of this disease is high. Further research on the association between depression and MS may lead to a better understanding of this relation. ■

Contributorship Statement / Declaração de Contribuição

AS, ÂS and ES: Acquisition of the data, interpretation of the data, writing the manuscript, manuscript review and final approval.

CF and RL: Manuscript review and final approval.

Responsabilidades Éticas

Conflitos de Interesse: Rita Lau e Catarina Flores são funcionárias da Biogen Portugal; Ernestina Santos declara ter recebido pagamento por consultoria, comunicações orais, despesas de deslocação ou como perita em diversas ações por parte das seguintes empresas: Genzyme, Novartis, Biogen, Alexion.

Os restantes autores declararam a inexistência de conflitos de interesse na realização deste trabalho.

Fontes de Financiamento: O estudo foi financiado pela Biogen Portugal.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: Rita Lau and Catarina Flores are employees of Biogen Portugal; Ernestina Santos declares that she has received payment for consultancy, oral communications, travel expenses or as an expert in various actions from the following companies: Genzyme, Novartis, Biogen, Alexion.

The other authors have declared no conflicts of interest in carrying out this work.

Financing Support: The study was financially supported by Biogen Portugal.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

- Hemmer B, Nessler S, Zhou D, Kieseier B, Hartung HP. Immunopathogenesis and immunotherapy of multiple sclerosis. *Nat Clin Pract Neurol*. 2006;2(2):201–11.
- Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple Sclerosis. *N Engl J Med*. 2000;343:938–52.
- Rudick RA, Sandrock A. Natalizumab: 4-integrin antagonist selective adhesion molecule inhibitors for MS. *Expert Rev Neurother*. 2004;4:571–80.
- Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galotta SL, Radue E-W, et al. Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354:911–23.
- Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vecsei L, et al. The epidemiology of multiple sclerosis in Europe. *Eur J Neurol*. 2006;13:700–22.
- Group GC. The Goldman Consensus statement on depression in multiple sclerosis. *Mult Scler J*. 2005;11:328–37.
- World Health Report. Mental Health, New Understanding, New Hope. Geneva: World Health Organization; 2001.
- Minden SL, Feinstein A, Kalb RC, Miller D, Mohr DC, Patten SB, et al. Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82:174–81. doi: 10.1212/WNL.000000000000013.
- Pandya R, Metz L, Patten SB. Predictive Value of the CES-D in Detecting Depression Among Candidates for Disease-Modifying Multiple Sclerosis Treatment. *Psychosomatics*. 2005;46:131–4.
- Fisk JD, Morehouse SA, Brown MG, Skedgel C, Jock Murray T. Hospital-based Psychiatric Service Utilization and Morbidity in Multiple Sclerosis. *Can J Neurol Sci*. 1998;25:230–5.
- Di Legge S, Piattella MC, Pozzilli C, Pantano P, Caramia F, Pestalozza IF, et al. Longitudinal evaluation of depression and anxiety in patients with clinically isolated syndrome at high risk of developing early multiple sclerosis. *Mult Scler J*. 2003;9:302–6.
- Arnett PA, Barwick FH, Beeney JE. Depression in multiple sclerosis: review and theoretical proposal. *J Int Neuropsychol Soc*. 2008;14:691–724. doi: 10.1017/S1355617708081174.
- Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. The burden of mental comorbidity in multiple sclerosis: frequent, underdiagnosed, and undertreated. *Mult Scler J*. 2009;15:385–92.
- Raskind MA. Diagnosis and treatment of depression comorbid with neurologic disorders. *Am J Med*. 2008;121:S28–37.
- Paparrigopoulos T, Ferentinos P, Kouzoupis A, Koutsis G, Papadimitriou GN. The neuropsychiatry of multiple sclerosis: Focus on disorders of mood, affect and behaviour. *Int Rev Psychiatry*. 2010;22:14–21. doi: 10.3109/09540261003589323.
- Göksel Karatepe A, Kaya T, Günaydn R, Demirhan A, Çe P, Gedizlioglu M. Quality of life in patients with multiple sclerosis. *Int J Rehabil Res*. 2011;34:290–8. doi: 10.1097/MRR.0b013e32834ad479.
- Feinstein A. Multiple sclerosis, depression, and suicide. *BMJ*. 1997;315:691–2.
- Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol*. 1997;54:531–3.
- Tarrant M, Oleen-Burkey M, Castelli-Haley J, Lage MJ. The impact of comorbid depression on adherence to therapy for multiple sclerosis. *Mult Scler Int*. 2011;2011:271321. doi: 10.1155/2011/271321.
- Feinstein A, Magalhaes S, Richard J-F, Audet B, Moore C. The link between multiple sclerosis and depression. *Nat Rev Neurol*. 2014;10:507–17. doi: 10.1038/nrneurol.2014.139.
- Vattakatuchery JJ, Rickards H, Cavanna AE. Pathogenic Mechanisms of Depression in Multiple Sclerosis. *J Neuropsychiatry Clin Neurosci*. 2011;23:261–76. doi: 10.1176/jnp.23.3.jnp261.
- Weiland TJ, Jelinek GA, Marck CH, Hadgkiss EJ, van der Meer DM, Pereira NG, et al. Clinically significant fatigue: prevalence and associated factors in an international sample of adults with multiple sclerosis recruited via the Internet. Reindl M, editor. *PLoS One*. 2015;10:e0115541. doi: 10.1371/journal.pone.0115541.
- Solaro C, Bergamaschi R, Rezzani C, Mueller M, Trabucco E, Bargiggia V, et al. Duloxetine is effective in treating depres-

- sion in multiple sclerosis patients. *Clin Neuropharmacol.* 2013;36:114–6. doi: 10.1097/WNF.0b013e3182996400.
24. Penner I-K, Bechtel N, Raselli C, Stöcklin M, Opwis K, Kappos L, et al. Fatigue in multiple sclerosis: relation to depression, physical impairment, personality and action control. *Mult Scler J.* 2007;13:1161–7.
 25. Lana-Peixoto MA, Teixeira AL, Haase VG. Interferon beta-1a-induced depression and suicidal ideation in multiple sclerosis. *Arq Neuropsiquiatr.* 2002;60:721–4.
 26. Seggar LB, Lambert MJ, Hansen NB. Assessing clinical significance: Application to the beck depression inventory. *Behav Ther.* 2002;33:253–69.
 27. MAPI Research Institute. [Accessed Jan 2022] Available at: <http://www.mapi-institute.com/>
 28. Meneses RF, Ribeiro JP M da SA. Subjective daytime sleepiness in a Portuguese clinical sample: Contribution for the study of the Epworth Sleepiness Scale. *Vigilia-Sueño.* 2001;13.
 29. Pais-Ribeiro J, Rodrigues AP. Questões acerca do coping: A propósito do estudo de adaptação do Brief Coping. *Psicol Saúde Doenças.* 2004;5:3–15.
 30. Guerreiro MS, Botelho MA. Adaptação à população portuguesa da tradução do “Mini Mental State Examination” (MMSE). *Rev Port Neurol.* 1994;9:9–10.
 31. Cetin K, Johnson KL, Ehde DM, Kuehn CM, Amtmann D, Kraft GH. Antidepressant use in multiple sclerosis: epidemiologic study of a large community sample. *Mult Scler J.* 2007;13:1046–53.
 32. Mohr DC, Hart SL, Fonareva I, Tasch ES. Treatment of depression for patients with multiple sclerosis in neurology clinics. *Mult Scler J.* 2006;12:204–8.
 33. Hind D, Cotter J, Thake A, Bradburn M, Cooper C, Isaac C, et al. Cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: a systematic review and meta-analysis. *BMC Psychiatry.* 2014;14:5. doi: 10.1186/1471-244X-14-5.
 34. Koch MW, Glazenborg A, Uyttenboogaart M, Mostert J, De Keyser J. Pharmacologic treatment of depression in multiple sclerosis. *Cochrane Database Syst Rev.* 2011;2011;CD007295. doi: 10.1002/14651858.CD007295.pub2.
 35. Schiffer RB, Wineman NM. Antidepressant pharmacotherapy of depression associated with multiple sclerosis. *Am J Psychiatry.* 1990;147:1493–7.
 36. Ehde DM, Kraft GH, Chwastiak L, Sullivan MD, Gibbons LE, Bombardier CH, et al. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. *Gen Hosp Psychiatry.* 2008;30:40–8.
 37. Silberberg D, Armstrong R. Tranylcypromine in multiple sclerosis. *Lancet.* 1965;2:852–3.
 38. Dean G. A double-blind trial with an antidepressant drug, imipramine, in multiple sclerosis. *S Afr Med J.* 1969;43:86–7.
 39. Scott TF, Nussbaum P, McConnell H, Brill P. Measurement of treatment response to sertraline in depressed multiple sclerosis patients using the Carroll scale. *Neurol Res.* 1995;17:421–2.
 40. Barak Y, Ur E, Achiron A. Moclobemide Treatment in Multiple Sclerosis Patients With Comorbid Depression. *J Neuropsychiatry Clin Neurosci.* 1999;11:271–3.
 41. Shafey H. The effect of fluoxetine in depression associated with multiple sclerosis. *Can J Psychiatry.* 1992;37:147–8.
 42. Thomas PW, Thomas S, Hillier C, Galvin K, Baker R. Psychological interventions for multiple sclerosis. *Cochrane Database Syst Rev.* 2006;2006:CD004431. doi: 10.1002/14651858.CD004431.pub2.
 43. Zephir H, De Seze J, Stojkovic T, Delisse B, Ferriby D, Cabaret M, et al. Multiple sclerosis and depression: influence of interferon b therapy. *Mult Scler J.* 2003;9:284–8.
 44. Patten SB, Francis G, Metz LM, Lopez-Bresnahan M, Chang P, Curtin F. The relationship between depression and interferon beta-1a therapy in patients with multiple sclerosis. *Mult Scler J.* 2005;11:175–81.
 45. Schippling S, O’Connor P, Knappertz V, Pohl C, Bogumil T, Suarez G, et al. Incidence and course of depression in multiple sclerosis in the multinational BEYOND trial. *J Neurol.* 2016;263:1418–26. doi: 10.1007/s00415-016-8146-8.
 46. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownschieldle CM, Murray TJ, et al. Intramuscular Interferon Beta-1A Therapy Initiated during a First Demyelinating Event in Multiple Sclerosis. *N Engl J Med.* 2000;343:898–904. doi: 10.1056/NEJM200009283431301.
 47. Interferon P (Prevention of R and D by, Group beta-1a S in MSS. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet.* 1998;352:1498–504.
 48. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology.* 1993;43:655–61.
 49. Hunter SF, Agius M, Miller DM, Cutter G, Barbato L, McCague K, et al. Impact of a switch to fingolimod on depressive symptoms in patients with relapsing multiple sclerosis: An analysis from the EPOC (Evaluate Patient Outcomes) trial. *J Neurol Sci.* 2016;365:190–8. doi: 10.1016/j.jns.2016.03.024.