

Cognitive and neuropsychiatric disorders among MS patients from Latin America

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Abstract

Cognitive and neuropsychiatric disorders in patients with multiple sclerosis have been extensively documented. The focus of this review will be on cognitive and neuropsychiatric disorders in multiple sclerosis patients from Latin America, in the context of international literature. Multicentre studies carried out in Latin America have shown that 43% of the patients have cognitive impairment and 34.5% in early stages of the disease, 29% depression and 20.9% neuropsychiatric disorders. The profile of cognitive impairment corresponds to alterations in visual and verbal memory, in attention, in information processing speed and in verbal fluency. The neuropsychiatric profile showed disorders in anxiety, depression, apathy and irritability domains. In the region, there exist validations of the multiple sclerosis neuropsychological screening questionnaire (MSNQ), the brief repeatable battery of neuropsychological tests (BRB-N) and the brief international cognitive assessment for multiple sclerosis (BICAMS), as well as of the paced auditory serial addition test (PASAT) and the symbol digit modalities test (SDMT). A study showed that 53% of the patients who met the NEDA3 condition had cognitive impairment. This finding highlights the need for taking cognitive assessment into account when determining therapeutic efficacy.

Keywords: Cognition, neuropsychiatric disorders, multiple sclerosis, Latin America, BICAMS, cognitive assessment

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Introduction

Cognitive and neuropsychiatric disorders in patients with multiple sclerosis (MS) have been widely investigated. Studies about the profile and prevalence of such disorders mostly come from North America and western Europe,^{1,2} but lately a few studies have appeared in Latin America (LATAM) reporting results specific to the region.^{3–6}

It is important to have regional data, because culture impacts cognitive performance and thoughts,⁷ as well as verbal and non-verbal tasks, as has been documented.⁸

The focus of this review will be on cognitive and neuropsychiatric disorders in MS patients from LATAM, in the context of international literature. In particular, the following topics will be developed: (a) profile and prevalence of cognitive impairment; (b) cognitive assessment; (c) role of cognitive

impairment in the concept of ‘no evidence of disease activity’ (NEDA); and (d) neuropsychiatric disorders.

Research was carried out in Pubmed, Scopus and Scielo databases. In Cochrane, Pubmed and Scopus we searched for the words ‘multiple sclerosis’ and ‘LATAM’ combined with any of these options: ‘cognitive disorders’, ‘neuropsychological disorders’, ‘cognitive assessment’, ‘neuropsychological assessment’, ‘neuropsychiatric disorders’, ‘psychiatric disorders’ and ‘depression’. In Scielo we searched for ‘esclerosis múltiple’ and ‘América Latina’ combined with any of the following: ‘desórdenes cognitivos’, ‘desórdenes neuropsicológicos’, ‘evaluación cognitiva’, ‘evaluación neuropsicológica’, ‘desórdenes neuropsiquiátricos’, ‘desórdenes psiquiátricos’ and ‘depresión’. Results were obtained up to April 2017. Papers published in English and Spanish were reviewed. Further articles were

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identified from the reference sections of these publications. The evidence obtained in the articles is presented here.

Prevalence of cognitive impairment

Epidemiological validations report that the frequency of cognitive impairment in patients with MS is 40–70%.^{9,10} These findings are based on studies carried out in North America and Europe, but in LATAM only a few investigations have been published on the subject. One of them is a cognitive impairment survey on MS patients carried out in Argentina by Cáceres et al.,³ where they found that 46% of the patients had cognitive impairment. It was a descriptive multicentre cross-sectional epidemiological study, in which 28 centres participated from eight different provinces from Argentina; 111 MS patients and 222 healthy controls were studied and the results obtained are similar to those found in other literature.^{3,11}

In Mexico, Macías-Islas et al. studied 177 MS patients and 177 control subjects recruited in the city of Guadalajara, a sample representative of the western part of the country. They found that 64% of the patients had cognitive impairment.

LATAM boasts the only multicentre study on cognition and neuropsychiatric disorders, called Relaccem (Spanish acronym for cognitive and behavioural survey of MS patients from LATAM). Fourteen centres specialising in MS from Argentina, Chile, Colombia, Venezuela, Uruguay and Mexico participated in the study, including 110 patients with relapsing–remitting multiple sclerosis (RRMS), with up to 5 years of disease evolution. That study showed that 34.5% of the patients had cognitive impairment,⁴ consistent with other early MS disease samples.¹²

Profile of cognitive impairment

At an international level, there is a general consensus about the nature of cognitive impairment in patients with MS. Studies show that recent memory, attention, information processing speed, visuospatial skills and executive functions are the areas most affected in the patient, while language and the intellect are seldom impacted.^{9,13,14} In 1999 in Brazil, Andrade et al.¹⁵ conducted one of the first studies on the topic. Although they studied a small sample of patients, they found that there exist disorders in attention and immediate and long-term verbal memory, which is partially in accordance with previous international literature. Cáceres et al.³ found deficits in visual and verbal memory as well as in

attention, information processing speed and verbal fluency in MS patients. This Argentinian study is particularly relevant because it administered and validated the brief repeatable BRB-N,¹⁶ the specific battery for MS. In doing so, it consolidated the foundation for the administration in the region of batteries internationally established. From then on, it was possible to do comparisons with studies of other countries, and above all, other LATAM countries could use it to detect cognitive alterations in patients with MS. Macías-Islas et al.⁵ studied 177 patients from Mexico and also reported disorders in visual and verbal memory, attention, information processing speed and verbal fluency. Bruno et al.,¹⁷ when studying especially the executive functions in 54 patients, reported that 62% presented with deficits in this area.

In relation to the clinical forms of the disease, it is agreed internationally that cognitive impairment is present in every clinical form, from the clinically isolated syndrome to RRMS, secondary progressive multiple sclerosis (SPMS) or primary progressive multiple sclerosis (PPMS), but it is especially severe and more frequent in the last two.^{11,18} Macías-Islas et al.⁵ also found that in the progressive forms of the disease, patients had a lower statistically significant performance in immediate and delayed recall in verbal tasks, as well as in attention and information processing speed. In the study by Cáceres et al.³ cognitive impairment was more prevalent in the progressive forms of the disease than in the RRMS form, showing a statistically significant difference. In Argentina, Drake et al.¹⁹ focused on the mnemonic performance of 55 patients with RRMS and 23 patients with SPMS, and they found not only a greater deficit of impairment, but also of the components of the memory process. SPMS patients produced errors due to confabulations and showed lower performance in information acquisition and recall tasks, which is consistent with previous studies.²⁰

It is unfortunate that in LATAM, some patients fail to complete all educational levels, which can negatively affect their cognitive performance. In this respect, in the study by Macías-Islas et al.⁵ patients with more than 13 years of schooling obtained better scores, showing a statistically significant difference in every test that was administered. Cáceres et al.³ found similar results in their study: the group of patients who had cognitive impairment performed lower in the tests. Such findings may contribute to explaining the severity variability of the deficits and strengthen the hypothesis that the more years of

schooling a MS patient has, the more they are differentially protected. Sinay et al.²¹ found that school performance was poorer in subjects who then became patients. Benedict et al.²² showed that the years of schooling and reading performance helped predict cognitive decline over 5 years.

The influence of race in MS has been investigated worldwide. It has been observed that the disease is more prevalent in white people than in other populations, especially Caucasians from northern Europe.²³ Several studies suggest that race is also associated with the clinical phenotype and the severity of this demyelinating disease.²⁴ From the clinical point of view, Caucasians have delayed symptom onset compared to Latin-American and African-American patients; for example, a larger proportion of Latin-Americans reported normal function for mobility and bladder/bowel function compared to Caucasians, and a larger proportion of Latin-Americans and African-Americans reported at least mild depression compared to Caucasians.²⁵ But there is little research about the influence of race on cognition. There is only a study by Weinstock-Guttman et al.,²⁶ in which African-American subjects with MS were evaluated by the New York State MS Consortium in a longitudinal study comprising more than 5600 patients. There it was found that cognitive impairment, as measured by the EDSS cerebral functional system score, developed earlier in the course of the disease in African-Americans compared with non-African Americans. In LATAM, different races are included, such as Amerindians (native Americans), Asians (people of Asian descent), Africans (African people), Mestizos (intermixing between Europeans and Amerindians), Mulattoes (people of mixed European and African ancestry), Caucasian or whites (European people) and Zambos (an admixture of black and Amerindian).²⁷ But in spite of these different races, according to guidelines of the race and ethnic standards for federal statistics and administrative reporting, Latin-American inhabitants are considered Hispanic. Hispanic being defined as 'a person of Mexican, Puerto Rican, Cuban, central or south American or other Spanish culture or origin, regardless of race'.²⁸ Likewise, the analysis of race and ethnicity is complicated because divisions blend genetics, culture, environment, education and potentially healthcare access.²⁹ In LATAM, the studies by Caceres et al.³ and Macías-Islas et al.⁵ showed a disease prevalence similar to what has been reported by international literature, but it is worth noting that the samples included Hispanic subjects. In the field of cognition in particular, although race and ethnicity

are relevant, other factors such as culture, education, language and environment must also be considered.³⁰

In more recent years, increasing attention has been paid to social cognition. In Argentina, Roca et al.³¹ showed deficits in cognitive theory of mind and Gleichgerrch et al.³² evidenced moral dilemmas, in relation to a high level of alexithymia and empathy disorders.

The relationship between cognitive impairment and quality of life has been studied in Argentina by Vanotti³³ in a group of 82 MS patients and 78 control subjects. Results showed that cognitive impairment has an impact in the patient's disease aspect – daily life activities and/or symptoms – as well as in the psychosocial aspect – relationships with family and friends and/or the sexual and emotional life. When analysing the differences between patients with and without cognitive impairment, it was observed that these are particularly related to the psychological wellbeing and relationships with friends. In addition, patients with MS have higher percentages of unemployment than has been reported in the literature.^{34,35} It is worth noting that more than 50% of the MS patients who have cognitive impairment are unemployed. Another unfortunate fact about the region is that a high percentage of patients with cognitive impairment belong to the lower classes.

Cognitive assessment

For the past three decades there has been an increasing production of batteries and tests that assess cognitive deficits of MS patients. Some of the reasons that may explain the tendency are: the fact that due to the high incidence of cognitive impairment, adequate assessment and diagnosis is essential;⁹ the fact that cognitive deficits may occur in one domain only, may vary over time and be subtle;⁹ and finally, the fact that the tests have to be administered with a certain degree of expertise, given that physical, visual or other sensory symptoms may affect cognitive performance.^{14,35,36} Cultural variables impact cognitive performance, especially in language.²⁹ It is for that reason that some studies have validated scales in Spanish and Portuguese in order to obtain appropriate detection instruments with the required psychometric characteristics.

Below there is a description of the tests and batteries most frequently used and their adaptations for LATAM ordered by form, such as disability scales,

self or informant-report questionnaires and screening batteries.

The first disability scale to take into account cognitive functions was the multiple sclerosis functional composite (MSFC). It was developed by a work group appointed by the National Multiple Sclerosis Society to review the assessment tests already in use and to produce recommendations for selecting an appropriate assessment scale for clinical trials.³⁷ The PASAT is one recommended test that has become the most used for this population worldwide. It specifically assesses working memory and information processing speed.^{38,39} Also recommended by the MSFC, it was initially developed by Gronwall,⁴⁰ and Rao later adapted it for use in MS, modifying the inter-stimulus interval to 3 and 2 seconds.¹⁶ In Argentina, Vanotti et al.⁴¹ validated the PASAT in a sample comprising 296 healthy subjects aged 20–70 years. One of the strengths of this study is that it was able to obtain a normative sample with an adequate degree of representation of different levels of instruction and ages. In it, the subjects' performance diminished as age increased, and it increased as the years of schooling were higher. This validation recruited subjects with little level of instruction – from 3 years of schooling onwards. Thus it is very useful for professionals who want to assess patients who have such instructional characteristics. Amato et al.⁴² and Boringa et al.⁴³ also found significant differences regarding the level of instruction of the patients. In addition, in Argentina Cores et al.,⁴⁴ following Coe et al.⁴⁵ and Fisk and Archibald,³⁹ analysed chunkings, a measure considered to be more sensitive than the analysis of the original score. In the Brazilian validation of the MSFC, the mean value of the PASAT is similar to that obtained in the Argentine validation.⁴⁶

For neurologists to be able to identify MS patients who could benefit from a formal or more comprehensive neuropsychological assessment, the MSNQ was developed.⁴⁷ It comprises 15 questions that the patient and an informant must answer. Vanotti et al.⁶ have validated this instrument through the multicentre project called Vanem (Spanish acronym for Argentina neuropsychological validation survey in MS patients), in a representative sample of 125 MS patients from Argentina.

In relation to screening tests, there are two cognitive batteries widely used in clinical and research contexts; both have good psychometric properties and have been constituted to be relatively robust to the effects of other MS symptoms.² These are the

BRB-N¹⁶ and the minimal assessment of cognitive function in multiple sclerosis (MACFIMS).¹⁴ The BRB-N was adapted by Cáceres et al.³ for Argentina. It includes the selective reminding test, the 7/24 spatial recall test, the PASAT and the word list generation. In the validation carried out in Argentina, the SDMT was also included. Thus, the BRB-N test includes instruments for measuring information processing speed, working memory, learning, verbal and visual memory and verbal fluency, which are all cognitive functions affected in patients with MS. Its administration time is approximately 25–30 minutes. This validation presented large effect sizes for the episodic memory, processing speed and working memory tests. Such effect sizes are similar to those found in previous studies.¹⁴ The MACFIMS battery was developed by the Consortium of Multiple Sclerosis Centers (CMSC) in April 2001, a group of specialists who selected the optimal tests to constitute a battery that could yield a global knowledge of cognitive processes. Like BRB-N, the MACFIMS battery consists of neuropsychological tests that assess information processing speed and working memory, learning and verbal memory, visuospatial processing and word formation, but the difference lies in the fact that MACFIMS also includes the study of executive functions. The selected tests were: the PASAT, SDMT, California verbal learning test II (CVLT II), brief visuospatial memory test-revised (BVMTR), Delis–Kaplan executive function system (D–KEFS), judgement of line orientation test and controlled oral word association test (COWAT). The administration time is 90 minutes.¹⁴ Unfortunately, this battery has not been validated in Spanish or Portuguese.

As the above-mentioned batteries demand time, are expensive and need to be administered by trained neuropsychologists,¹⁰ another expert committee has developed BICAMS, an international assessment tool used to monitor cognitive function in MS patients.⁴⁸ Its administration time is approximately 15 minutes. It was designed and optimised for small centres where health professionals may not have neuropsychological training, and for international usage so as to facilitate comparison across settings.⁴⁹ It includes three tests of high reliability and sensitivity: Rao's adaptation¹⁰ of the SDMT,⁵⁰ the initial learning trials of the CVLT II⁵¹ and the BVMTR.⁵² International validations are currently underway and up to now normative data exist for a number of countries.^{53–57} Fortunately, as per LATAM, Spedo et al.⁵⁸ and Vanotti et al.⁵⁹ have validated this battery for Brazil and Argentina, respectively. Both

Table 1. Mean raw scores of the MS patients and the healthy control participants in the Brazilian and Argentine versions of the BICAMS battery.

	SDMT		CVLT		BVMT-R	
	MS patients	HC	MS patients	HC	MS patients	HC
Spedo et al. ⁵⁸	35.9 ± 16.1	47.5 ± 13	42.1 ± 12.4	53.4 ± 10.8	19.9 ± 8.6	23.8 ± 7.7
Vanotti et al. ⁵⁹	45.14 ± 16.07	56.71 ± 10.85	50.92 ± 12.37	60.88 ± 10.46	20.70 ± 7.74	23.44 ± 5.84

MS: multiple sclerosis; BICAMS: brief international cognitive assessment for multiple sclerosis; SDMT: symbol digit modalities test; CVLT: California verbal learning test; BVMT-R: brief visuospatial memory test revised; HC: healthy controls.

validations showed significant differences between MS patients and healthy controls as well as adequate psychometric properties, thus constituting reliable and valid studies for the region. Table 1 describes the characteristics of BICAMS validations in LATAM.

In Brazil, Negreiro et al.⁶⁰ proposed the verbal fluency, Rey auditory verbal learning and enhanced cued recall tests to constitute a brief battery representing the first Brazilian MS cognitive screening. However, from authors' comments, further validation study is necessary to achieve better normative scores.

Currently, the SDMT is considered to be the best instrument for assessing information processing speed.⁶¹ Historically, both the PASAT and SDMT have been used because they were part of the BRB-N and MACFIMS batteries, but the SDMT has proved to be more reliable and sensitive, as well as more accepted by the patient.^{62,63} The SDMT is currently the leading cognitive test candidate of the more recent effort of the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) to qualify performance scales for clinical trials of MS.⁶¹ In Argentina, Vanotti et al.⁶⁴ validated this test with a sample of 297 healthy participants, and as some of the participants who were recruited had few years of schooling, the test proved to be useful for clinical consultation, similar to the case of the PASAT. Regarding culture and its importance, Cores et al.⁶⁵ have compared the performance of two groups in the SDMT: a sample of 137 healthy subjects from America and 137 healthy participants from Argentina, and found that the latter performed less well than the former. This result suggests that the cultural values of the participants need to be taken into account when analysing the performance of different populations. Table 2 describes the tests and batteries validated in Spanish, and in

Table 3 there is a list of evidence of the populations who were assessed in LATAM, in addition to the cognitive functions affected.

Role of cognitive impairment in the concept of NEDA

The appearance of a wide array of immunomodulatory drugs for treating MS has resulted in the need for evaluating the efficacy of such drugs. Whereas the primary outcomes of pivotal studies never included cognitive or neuropsychiatric impairment, the number of relapses, the progression of motor disability and the findings through magnetic resonance imaging (MRI) – related to the number of injuries and their activity – have been considered the main elements to measure the efficacy of immunomodulatory treatments.⁶⁶

In recent years, that was redefined in the concept of NEDA, considered to be more appropriate when establishing the therapeutic efficacy of those treatments.^{67,68} However, some studies question this concept as a parameter of efficacy consistent in time, and they argue that it lacks comprehensiveness because it does not include other aspects of MS, such as cognitive compromise and brain atrophy.^{69,70} In this respect, Damasceno et al.⁷¹ conducted a recent study in which they evaluated 42 MS patients and 30 control subjects from Brazil. Patients were studied in the three classic parameters of NEDA3: relapses, progression of motor disability and MRI activity, but they were also assessed regarding cognitive function and brain atrophy. The patients' cognitive function was evaluated with BRB-N and SDMT, and the brain atrophy was measured in volumetric T1 images by means of the FreeSurfer v.5.1 (<http://surfer.nmr.mgh.harvard.edu/>); 38.9% of the patients were treated with intramuscular interferon (IFN) β -1a, 38.9% with subcutaneous IFN β -1b and 22.2% with glatiramer acetate. The assessments were carried out at base level and at the first and

Table 2. Demographics data and characteristics of the batteries validated in Spanish in LATAM.

	BRB-N ³	BICAMS ⁵⁹	MSNQ ⁶	PASAT ⁴¹	SDMT ⁶⁴
MS patients, <i>n</i>	111	50	125	—	—
HC, <i>n</i>	121	100	34	296	297
Mean age: years ± SD	MS 40.9 ± 11.3	MS 43.42 ± 10.17	MS 42.3 ± 10.5	43.95 ± 16.31	39.28 ± 11.69
HC 41.12 ± 9.13	HC 42.37 ± 10.07	HC 33.2 ± 10.2			
Mean education: years ± SD	MS 13.65 ± 2.55	MS 14.86 ± 2.78	MS 13.7 ± 3.4	11.69 ± 4.42	13.67 ± 3.51
HC 13.8 ± 3.1	HC 13.1 ± 3.9	HC 13.1 ± 3.9			
% of Women	MS 83.2%	MS 74%	MS 67.2%	64.52%	77.7%
HC 82.9%	HC 75%	HC 75%			
Disease evolution	MS 7.4 ± 7.0	MS 13.06 ± 9.08	MS 8.8 ± 7.0	—	—
EDSS	—	MS 3.29 ± 2.55	MS 3.3 ± 2.3	—	—
Tests	Selective reminding test	Symbol digit modalities	Patient self-report	—	—
	7/24 Spatial recall test	California verbal learning test	Informant-report	—	Oral version
	Word list generation	Brief visual memory test —revised			
	PASAT 2 and 3'				

LATAM: Latin America; BRB-N: brief repeatable battery of neuropsychology test; BICAMS: brief international cognitive assessment for multiple sclerosis; MSNQ: multiple sclerosis neuropsychological screening questionnaire; PASAT: paced auditory serial addition test; SDMT: symbol digit modalities test; MS: multiple sclerosis; HC: healthy controls; SD: standard deviation; EDSS: Expanded Disability Status Scale.

second year. Only 30% of the patients obtained the NEDA3 condition. Of them, 58% showed cognitive impairment in BRB-N and 25% showed more than four points of impairment in SDMT. Patients who presented MRI activity had more cortical thinning and a slight decrease in thalamus volume. Those findings question the accuracy of NEDA3 for establishing therapeutic success, and they suggest the need to include other elements of clinical importance in the concept.

Also in this line of debate, there exist other proposals ‘beyond the concept of NEDA’, including depression and anxiety, as well as others related to MS, such as fatigue and quality of life.⁷²

Neuropsychiatric disorders

It is widely documented that patients with MS have a higher risk of experiencing emotional disorders. These include major depressive disorder, bipolar disorder, pathological euphoria and emotional incontinence – involuntary crying or uncontrollable episodes of crying and/or laughing, and less frequently, obsessive–compulsive disorder and psychotic disorder.⁷³

Depression is the most frequent disorder among these patients. Its prevalence along the life of MS patients is estimated at more than 50%, and its annual prevalence, compared to the general population, is three to 10 times higher.⁷⁴ The results reported by Minden et al.⁷³ confirm that estimation, pointing out that the prevalence rates of the major depressive disorder rise up to 36–54%, against 16.2% in the general population. Marrie et al.⁷⁵ also showed that anxiety has a prevalence of 21.9%.

In LATAM, the Relacem project is the only multi-centre study that studied neuropsychiatric disorders in patients with less than 5 years of disease evolution. In a sample of 110 patients, they found that scores from Beck’s depression inventory II (BDI-II) were significantly higher compared with those of the control subjects, which is in accordance with previous literature. In addition, in the administration of the neuropsychiatric inventory (NPI), significant differences were found regarding anxiety, depression, apathy and irritability. It was found that 29% of the patients showed signs of impairment in BDI-II, and that 20.9% showed anomalies in NPI.⁴ This symptomatology has been reported in other studies of later stages of the disease, but not in initial stages.^{76,77} Particularly interesting is that in the Relacem study, the caregiver burden in MS was analysed by the Zarit scale.⁷⁸ Even though such a scale is administered specifically in senior patients,

Table 3. Description of studies carried out in LATAM.

	Country	MS patients	Domains
Andrade et al. ¹⁵	Brazil	25	Intelligence/memory/perceptual/motor capacities/language/mood
Bruno et al. ¹⁷	Argentina	54	Executive function
Cáceres et al. ³	Argentina	111	Verbal and visual memory/attention/information processing speed/verbal fluency
Cáceres et al. ¹²	Argentina, Chile, Columbia, Venezuela, Uruguay, Mexico	110	Verbal and visual memory/attention/information processing speed/verbal fluency Neuropsychiatric symptoms
Drake et al. ¹⁹	Argentina	55	Memory
Gleichgerrch et al. ³²	Argentina	38	Alexithymia/empathy/moral dilemmas
Macías-Islas et al. ⁵	Mexico	177	Verbal and visual memory/attention/information processing speed/verbal fluency
Negreiro et al. ⁶⁰	Brazil	54	Verbal fluency/memory
Roca et al. ³¹	Argentina	18	Theory of mind
Vanotti et al. ⁶	Argentina	125	Perception cognitive difficulties – self-report questionnaire
Vanotti ³³	Argentina	82	Verbal and visual memory/attention/information processing speed/verbal fluency/quality of life
Vanoti et al. ⁵⁹	Argentina	50	Verbal and visual memory/information processing speed

LATAM: Latin America; MS: multiple sclerosis.

it was selected in the absence of another scale validated in Spanish for such purposes, up to the moment when the patients were enrolled. Despite the lack of sensitivity of the scale, significant differences were found between patients with MS and the control group. Within the group of MS patients, linear regression controlling for demographics was used to determine the most important cognitive and neuropsychiatric predictors of caregiver burden, and the model retained the disinhibition of the NPI and BDI-II. The presence of neuropsychiatric disorders points towards the need for appropriate and early interventions to mitigate the psychosocial consequences of caregiver burden.⁴

In Mexico, Díaz Olavarrieta et al.⁷⁹ also analysed a sample of 44 patients with the NPI, and found that the domains with more deficit prevalence were depression, agitation, anxiety and irritability.

Neuropsychiatric disorders, when not detected or treated, can affect the patients' functioning and

quality of life, reduce adherence to the treatment and increase the risk of suicide.⁷⁴ Epidemiological data suggest that the standardised mortality ratio for suicide in MS patients approximately doubles that of the general population. Depression, social isolation and alcohol abuse are all associated with suicide thoughts.⁸⁰ Unfortunately, the region lacks suicide records, as well as records of the causes that may trigger suicide thoughts.

Conclusions

In LATAM there are three multicentre studies: two from Argentina (Reconem and Vanem), and another that includes six countries of the region (Relaccem). Such studies produced regional data related to the prevalence and the profile of cognitive impairment and neuropsychiatric disorders. They also validated scales and batteries of cognitive tests, necessary for detecting cognitive impairment, particularly in those patients with fewer years of schooling. The caregiver burden has also been mentioned with a high degree

of importance, related to the presence of neuropsychiatric disorders.

A study showed that 53% of the patients who met the NEDA3 condition had cognitive impairment.

Few studies have been published in LATAM compared with North America and western Europe, which indicates that it is necessary to implement strategies for carrying out national and regional studies. There should be more focus on studying neuropsychiatric disorders and on considering the sociocultural variables of the region, as well as their implication in cognitive and neuropsychiatric impairment.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to this review.

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