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ARTICLE

ENCOMS: Argentinian survey in cost of illness and unmet needs in multiple sclerosis

ENCOMS: encuesta argentina sobre costos de la enfermedad y necesidades no cubiertas en pacientes con esclerosis múltiple

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ABSTRACT

The objective of the study was to assess the cost of multiple sclerosis (MS) patients in Argentina categorized by disease severity using a societal perspective. **Method:** Cross-sectional study including MS patients from 21 MS centers in 12 cities of Argentina. Patients were stratified by disease severity using the expanded disability status scale (EDSS) (group 1 with EDSS score between 0 and 3; group 2 with EDSS >3 and <7; group 3 with EDSS ≥7). Direct and indirect costs were analyzed for the second quarter of 2012 from public sources and converted to US Dollars. **Results:** 266 patients were included. Mean annual cost per MS patient was USD 36,025 (95%CI 31,985-38,068) forts patients with an EDSS between 0-3; USD 40,705 (95%CI 37,199-46,300) for patients with EDSS >3 and <7, and USD 50,712 (95%CI 47,825-62,104) for patients with EDSS ≥7. **Conclusions:** This is the first Argentine study evaluating the costs of MS considering disease severity.

Keywords: multiple sclerosis, costs, cost-of-illness, Argentina, Latin America.

RESUMO

El objetivo del estudio fue evaluar el costo de los pacientes con esclerosis múltiple (EM) en Argentina categorizados por severidad de la enfermedad. **Método:** Estudio de corte transversal que incluyó pacientes con EM en 12 ciudades de Argentina. Los pacientes se estratificaron según *expanded disability status scale* (EDSS) (grupo 1 EDSS entre 0 y 3; grupo 2 EDDS >3 y <7; grupo 3 EDSS ≥7). Los costos directos e indirectos fueron analizados para el segundo trimestre de 2012 y convertidos a dólares estadounidenses. **Resultados:** 266 pacientes fueron incluidos. El coste medio anual por paciente con EM fue de USD 36,025 (31,985-38,068 IC95%) para los pacientes con un EDSS entre 0-3; USD 40,705 (37,199-46,300 IC95%) para los pacientes con EDSS >3 y <7 y USD 50,712 (47,825-62,104 IC95%) para los pacientes con EDSS ≥7. **Conclusiones:** Primer estudio argentino evaluar los costes de la EM considerado la gravedad de la enfermedad.

Palavras-chave: esclerosis múltiple, costos, enfermedad, Argentina, Latino-América.

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Multiple sclerosis (MS) is the second most common cause of neurological disability in working-age population, after car accidents, having an impact on quality of life, social activities and also the environment of affected patients[1]. The course of the disease is highly variable, but it is most typically characterized by a relapsing pattern of acute exacerbations followed by periods of remission (relapsing-remitting MS [RRMS]). However, in up to 50% of patients, this pattern evolves into a progressive course in which the clinical condition slowly deteriorates over the years (secondary progressive MS [SPMS])[2]. Considering the natural course of this disease, the progressive physical disability carries hard economic consequences from the early loss of work capacity[3,4]. MS patients required repeated hospitalizations during disease exacerbations and the need of assistance in daily life activities, being the socioeconomic cost of the disease high for patients, families, health care systems and society as a whole[4].

Mean total lifetime cost per patient of MS in the US was estimated to be USD 2.5 millions in 1994[5], and some publications have addressed MS epidemiology and costs worldwide[6,7,8,9,10,11]. Nonetheless, current knowledge of MS epidemiology and economic burden comes from North American and European studies[9,10,12,13].

In Argentina, reported prevalence rates of MS range between 16 to 21 cases per 100,000 inhabitants[9,14,15]. Despite this information, the economic burden associated with the disease in Argentina as well as in the region of Latin America, is unknown.

In order to better understand the impact of the disease on national health systems in the region, the objective of the study was to measure the socioeconomic burden that MS imposes to the Argentine society by disease severity and to contribute detailed cost information in the country.

METHOD

Study design

The Treatment Experience, Burden and Unmet Needs in Multiple Sclerosis Study (ENCOMS) in Argentina was an adaptation of the successful experience of TRIBUNE performed in several European countries and Canada[16,17,18,19,20], but using validated questionnaires for Argentina. The study was then a national, cross-sectional, observational and retrospective study including MS patients from 21 MS centers in 12 cities of Argentina. It was conducted to collect information on demographics, disease characteristics, disease severity, comorbidities, relapses as well as resource utilization and patient reported outcomes (PRO) associated with MS (ICD-10; G35, ICD-9; 340). Cities involved in the study were: Buenos Aires, Salta, Mendoza, Córdoba, Santa Cruz and Ushuaia. The study began in August 2011 and enrollment ended in February 2012. Site staff identified eligible patients by screening patient records, and an invitation to participate in the study was sent to patients who met the inclusion criteria (MS diagnosis[21,22,23] and at least 18 years old). Patients having any physical or mental condition making them ineligible to participate or were already enrolled in other clinical trial were excluded. The study protocol and questionnaire were approved by the Ethics Committee prior to the initiation of the study.

Assessments

Patients self-completed a written-questionnaire in Spanish during enrolment interview. Patients provided information on: age, sex, living arrangements, educational level, employment status, and informal caregiver(s). Disease information including year of diagnosis, year of first symptoms, type of MS, disability (captured using the self-administered Expanded Disability Status Scale (EDSS)[24]), comorbidities (arthritis, osteoporosis, depression, anxiety, sleep disorders, hypertension and urinary tract infections/incontinence) and treatment with disease modifying drugs (DMDs) was also captured. The disability scale version used in the study was the modified and validated version that had been previously used in other cost-of-illness studies in MS[20]. Patients were asked about relapses experienced in the last 12 months, including occurrence and number of relapses, number of those requiring steroid treatment and number of days of inpatient care for relapses.

Resource utilization

Data on healthcare including inpatient and outpatient care, magnetic resonance imaging (MRI) studies performed, consultations with medical practitioners, treatment with DMDs, prescription and over-the-counter medication as well as non-medical resources used (wheelchairs), professional and informal care and patients' productivity loss (sick leave

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and retirement due to the disease), was collected using the questionnaire. Different recall periods were used for different resources. Hospital stays, investigations/MRIs and use of wheelchair were recorded for the previous year. A 3-month recall period was used for outpatient admissions, consultations with hospital-based or private practice physicians, use of DMDs, services such as home care and nursing, informal care by family and friends, and absences from work due to sickness. Patients were asked to report the use of co-medication and over-the-counter medication during the last month.

Costs

To obtain the cost per patient per year, resources used were first annualized assuming that the use of each resource during the recall period was representative of the patients' use during a whole year. The annual use of each resource was multiplied by its respective unit cost to get the annual cost. Second quarter 2012 unit costs were derived from public sources of Argentina including the *Instituto Nacional de Estadísticas y Censos*[25] (Indec), the *Nomenclador Nacional*[26], drugs public price list[27] and, when necessary, costs from the Sanitary and Clinical Effectiveness Institute (IECS) cost database[28]. Unit cost in Argentine pesos was converted to US dollars using June 2012 exchange rate (USD 1=AR$ 4.46). Costs are shown in Table 1. The cost of sick leave was calculated by multiplying the patient-reported days lost from work due to MS by the average gross salary per day. To estimate productivity losses of early retirement due to MS, the mean annual number of hours worked in 2011 in Argentina was multiplied by the gross salary[20]. Informal care was rated using productivity loss of the working caregiver, multiplied by the average gross salary. In order to asses only the hours leading to informal caregiver productivity loss, the average working hours per week were considered[19,20].

Table 1. Unit costs in US Dollars (June 2012).

Unit costs	US dollars
Interferon beta 1 a SC (monthly cost)	4212
Interferon beta 1 a IM (monthly cost)	3366
Interferon beta 1 b (monthly cost)	3473
Copaxone (monthly cost)	3714
Natalizumab (monthly cost)	4302
Professional care (hour)	7
Wheelchair	304
Informal care (hour)	7
Antidepressant treatment (month)	28
Anti-spasticity medication (month)	13
Cognition medication (month)	46
Fatigue medication (month)	19
Sleep medication (month)	11
Urinary dysfunction medication (month)	25
Sick leave (day)	54
Retirement due to multiple sclerosis	13826

Statistical analysis

Patients were stratified according to disease severity using the EDSS (group 1 with EDSS between 0 and 3; group 2 with EDSS >3 and <7; group 3 with EDSS ≥7) for the analysis. Use of resources was determined for each group and cost was obtained from the estimated resource utilization. Confidence intervals (95%) for costs were estimated by non-parametric bootstrapping. A non-parametric statistical test for independent samples (Wilcoxon-Mann-Whitney test) was used to determine whether differences between comparisons performed were statistically significant (p-value<0.05).

RESULTS

Patient characteristics

A total of 266 patients were enrolled. Mean age of patients enrolled was 42.3±10.5 years, Reported mean age at the onset of the disease was 31.6±9 years Almost 20% of patients had a university degree and 16.5% of patients were currently retired due to the disease. Most MS patients had the relapsing-remitting form of the disease (87.6%). When stratifying the sample included, 188 (70.7%) patients had an EDSS score between 0 and 3; 51 (19.2%) an EDSS >3 and <7 and 27 (10.1%) an EDSS ≥7). Patients with mild disability were younger than moderate or severe MS patients (p-value=0.007). The remaining patient characteristics including comorbidities, employment status and living situation are displayed in Table 2.

Resource utilization

The proportion of patients who received inpatient care, had medical visits and used co medications significantly increased across disability severity subgroups, being 10%, 27% and 100%, respectively, in patients with an EDSS ≥7, while the proportion of patients with MS-specific medication decreased from 77.1% to 51.8% in patients with EDSS between 0 and 3 and EDSS ≥7 respectively. Informal care was more frequently reported among patients with severe disability compared with patients with moderate and mild disability (100% vs. 61% vs. 21%, respectively). Almost 85% of patients with an EDSS ≥7 were retired due to MS. Other resource utilization by patients is shown in Table 3.

Costs

The mean cost per MS patient per year stratified by disability from a societal perspective was measured and is displayed in Table 4 and Figure. The mean cost of patients significantly increased across disability severity groups, being of USD 36,025 (95% confidence interval (CI) 31,985-38,068) in patients with an EDSS between 0 and 3, USD 40,705 (95% CI37,199-46,300) in patients with EDSS >3 and <7

Table 2. Baseline characteristics of multiple sclerosis (MS) patients enrolled.

Variable	N	% or SD
Number participants enrolled	266	-
Gender		
Male	83	31.2
Female	183	68.8
Age		
Mean current age	42.3	±10.5
Patients by current age cohorts		
18-29 years	39	14.7
30-39 years	64	24.1
40-49 years	76	28.6
50-59 years	84	31.8
60-69 years	3	1.13
Mean age at onset	31.6	±9
Patients by age at onset cohorts		
18-29 years	122	45.9
30-39 years	82	30.9
40-49 years	60	22.6
50-59 years	2	0.8
60-69 years	0	-
Living situation		
Alone	53	20
Family, spouse/partner	210	79
Nursing home	3	1
Education level		
Secondary school	154	57.9
Professional diploma	59	22.2
University degree	53	19.9
Employment situation		
Employed	144	54.3
Student	19	7.1
Unemployed	59	22.1
Retired due to MS	44	16.5
Informal caregiver		
At least one informal caregiver	181	70.4
Spouse or family member	156	58.7
Friend, neighbor	25	9.4
MS type		
Relapsing remitting	233	87.6
Secondary progressive	19	7.1
Primary progressive	14	5.3
Comorbidities		
Urinary incontinence	41	15.5
Sleep disorders	45	17
Arthritis	8	3
Hypertension	17	6.4
Cognitive disorders	48	18.1
Disease severity		
Mean EDSS score	2.6	±2.2
Number of patients by EDSS cohorts		
EDSS 0-1	96	36.1
EDSS 2-3	92	34.6
EDSS 4-5	39	14.7
EDSS 6-6.5	12	4.5
EDSS 7, 8 & 9	27	10.2
MS treatment		
Currently treated	206	77.4
Currently untreated but treated in the past	36	13.5
Treatment-naïve	24	9

SD: standard deviation; EDSS: expanded disability status scale; n: number of patients.

and USD 50,712 (95%CI 47,825-62,104) in patients with EDSS ≥7. In patients with EDSS ≥7, the cost for patients' sick leave and retirement due to MS was an important component, comprising 25.7% of total costs, while direct non-medical costs represented 21.6% of the total cost. Informal care was assessed on the base case analysis using only working caregiver productivity loss. In patients with EDSS ≥7, mean annual cost of informal care per patient represented 12.5% of the total annual cost per patient, while in patients with EDSS between 0 and 3 and >3 and <7, informal care represented 0.2% and 5.6%, respectively, of total costs. In patients with EDSS between 0 and 3, most of the cost came from direct medical costs including MS-specific medication.

DISCUSSION

The robust ENCOMS study showed that MS imposes a significant economic burden on Argentine society. Mean annual cost per patient was estimated at USD 36,025 in patients with an EDSS between 0 and 3 and reached USD 50,712 in patients with EDSS ≥7. This economic burden increases with higher physical disability. This was accounted for by the increase in resource utilization of medical visits, informal care, professional care, sick leave as well as retirement due to MS in the sample analyzed.

Our study is consistent with previous cost-of-illness studies performed in Canada[20] and some European countries[16,18,29]. In Canada, Karampampa et al. also demonstrated that increased physical disability was associated with increased direct and indirect costs partially explained by a higher need for medical and non-medical care associated with disability progression[20]. In the Canadian study, the mean annual cost per patient for 2009 was estimated at CAD 30,836 for patients with mild disability (EDSS score 0-3), CAD 46,622 for patients with moderate disability (EDSS 4-6.5), and CAD 77,981 for patients with severe disability due to MS (EDSS score 7-9)[20]. The increase in the economic burden of the disease associated with the increase in physical disability, was also showed by Karampampa et al in the European health care systems such as those from Spain, France, Germany and the United Kingdom[19].

In Argentina, this is the first study designed to capture the economic burden of the disease. In Latin America, a comprehensive cost study, from a third party payer perspective and including MS patients from 3 MS centers in the country was done by Romero et al in Colombia between 2003 and 2008[30]. The study estimated direct and indirect costs according to disease progression as measured by EDSS in MS patients. The disease was classified into 4 categories according to EDSS: category 1 EDSS 0-2.5, category 2 EDSS 3-5.5, category 3 EDSS 6-7.5, and category 4 EDSS 8-9.5) and costs for each category were estimated. The study showed that

Table 3. Resource utilization by EDSS.

	Unit	EDSS 0-3 (n=188)		EDSS 4-6.5 (n=51)		EDSS 7-9 (n=27)	
		% (n) of patients using resources	Mean (SD) use per patient per year	% (n) of patients using resources	Mean (SD) use per patient per year	% (n) of patients using resources	Mean (SD) use per patient per year
Inpatient care	days	2.1 (4)	3.7 (1.8)	5.7 (3)	2.8 (2.4)	37 (10)	7.9 (5)
Outpatient care	times	20.7 (39)	2 (3)	23.5 (12)	6 (4)	34 (9)	8 (5)
Consultations	visits	72 (135)	13 (15)	82.3 (42)	33 (17)	100 (27)	72 (68)
Investigations MRI	tests	59 (111)	1.4 (0.8)	62 (32)	1.3 (0.8)	48 (13)	1 (0.4)
Relapses requiring steroids treatment	days	14.3 (27)	4.1 (2.4)	47 (24)	4.3 (2.1)	18.5 (5)	4.5 (2.6)
MS treatments	n.a.	77.1 (145)	n.a.	70.5 (36)	n.a.	51.8 (14)	n.a.
Prescribed co-medication	days	35 (66)	135 (176)	68 (35)	389 (315)	100 (27)	734 (398)
Antidepressants	days	12 (23)	65 (34)	23.5 (12)	110 (56)	31 (8)	365 (178)
Anti-spasticity medication	days	5.7 (11)	35 (15)	25.5 (13)	145 (101)	38.5 (10)	278 (198)
Cognition medication	days	4 (8)	38 (27)	11.7 (6)	46 (32)	23.1 (6)	78 (24)
Fatigue medication	days	9.6 (18)	48 (19)	19.6 (10)	92 (54)	48 (13)	213 (132)
Sleep medication	dys	12.3 (23)	76 (44)	25.5 (13)	81 (35)	42 (11)	138 (72)
Urinary dysfunction medication	days	2.1 (4)	38 (10)	19.6 (10)	164 (106)	48 (13)	287 (163)
OTC drugs	n.a.	45 (85)	n.a.	59 (30)	n.a.	85 (23)	n.a.
Investments/modifications	n.a.	3.2 (6)	n.a.	22 (11)	n.a.	56 (15)	n.a.
Wheelchair	n.a.	0	n.a.	4 (2)	n.a.	85.2 (23)	n.a.
Professional care	hours	0	-	49 (25)	201 (145)	77.7 (21)	798 (655)
Informal care	hours	20 (38)	47 (10)	61 (31)	561 (235)	100 (27)	945 (756)
Sick leave	days	10 (19)	5.8 (2.4)	39.2 (20)	101 (88)	14.8 (4)	160 (142)
Retirement	n.a.	1.1(2)	n.a.	37.2 (19)	n.a.	85.1(23)	n.a.

EDSS: expanded disability status scale; MS: multiple sclerosis; MRI: magnetic resonance imaging; OTC: over the counter; SD: standard deviation.

the mean annual cost per patient varied across disease categories, with the highest cost in category 2 (USD 25,713) and the lowest one in category 4 (USD 10,543). The cost of DMDs accounted for 91.5% of the mean total annual cost for categories 1, 2 and 3. Indirect costs were minimal, except for category 4, where higher costs of DMDs were offset by lower use of DMDs[30]. Despite this valuable information, the study did not take into account some direct non-medical costs as well as indirect costs such as professional care, informal care, sick leave and retirement due to MS[30]. This

Table 4. Annual cost per patient by EDSS in 2012 US dollars, 95% confidence interval (CI).

	EDSS 0-3 (n=188)			EDSS 4-6.5 (n=51)			EDSS 7-9 (n=27)		
	Mean	SD	95%CI	Mean	SD	95%CI	Mean	SD	95%CI
Inpatient care	18	9	5-32	37	32	29-77	683	432	577-866
Outpatient care	72	108	58-98	245	164	188-365	473	296	336-702
Consultations	65	75	32-123	189	97	140-244	501	473	389-686
Investigations MRI	149	85	108-193	146	90	116-196	87	35	58-150
MS treatments	35,280	5,120	32,656-39,053	32,260	4,777	29,060-39,034	26,422	23,703	21,582-29,421
Relapses requiring steroid treatment	135	79	99-190	465	227	365-705	192	111	138-292
Prescribed co-medication	22	14	19-27	96	57	78-109	400	220	335-485
OTC drugs	36	50	29-62	84	64	67-201	698	389	426-991
Total direct medical costs	35,778	32,567	33,096-39,855	33,438	49,643	28,944-41,568	26,737	8,658	24,298-33,096
Wheelchair	0	0	n.a.	12	70	5-142	259	193	196-438
Professional care	0	0	n.a.	685	494	508-1933	4,310	3,538	2,772-5,289
Informal care	63	13	44-118	2,305	965	1,714-3405	6,364	5,091	5,115-7,992
Total direct non-medical costs	63	9	34-75	3,001	534	2,144-3785	10,933*+	3,670	7,896-14,189
Sick leave	31	13	16-42	2,133	1,859	1,567-2,647	1,276	1,132	944-1,953
Retirement	152	100	50-269	2,133	845	1,644-2,800	11,766	6,446	6,993-14,292
Total indirect costs	183	80	123-215	4,266	920	2,923-6,291	13,042*+	10,404	9,117-19,405
Total costs	36,025	7,991	31,985-38,068	40,705	8,773	37,199-46,300	50,712*+	5,337	47,825-62,104

*Difference is statistically significant compared to the mild subgroup of patients (p-value <0.05); +Difference is statistically significant compared to the mild subgroup of patients (p-value <0.05). EDSS: expanded disability status scale; MS: multiple sclerosis; MRI: magnetic resonance imaging; SD: standard deviation.

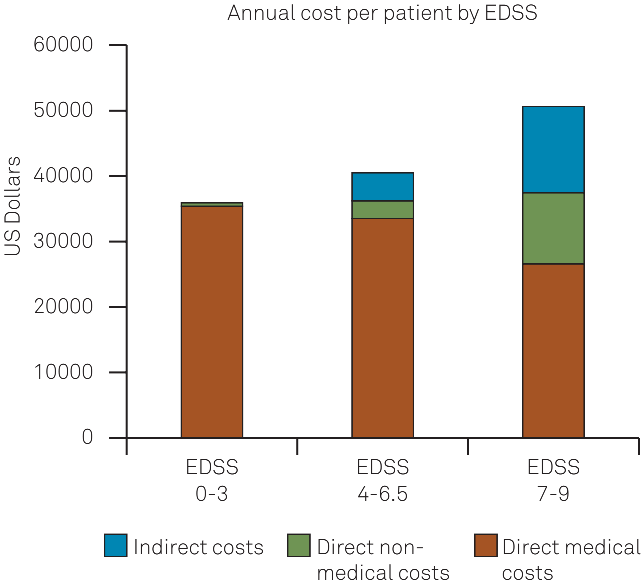

Figure. Annual cost per patient by expanded disability status scale (EDSS) in 2012 US dollars.

might explain the economic burden differences observed in patients with severe disability in the study by Romero and our findings. No other studies analyzing the economic burden of the disease, stratifying by physical disability and considering direct as well as indirect costs in the Latin American region were identified.

The study has many limitations. First of all, the sample involves patients from all disability spectrums; however, the proportion of patients with severe disability was lower in relation to patients with moderate and mild disability. Therefore, a larger sample would be necessary to generalize the results. Another limitation observed in previous studies on which ENCOMS was based[19] relates to the fact that cost estimates are likely to reflect how the sample of MS patients was derived. Cost estimates would probably have been lower if the sample had included MS patients recruited from the community rather than from specialized clinics. The above could lead to the fact that many patients are receiving MS-specific treatments as well as professional and informal care in relation to total MS population in Argentina. Despite this, we tried to overcome the possibility of bias by including patients from several MS centers from widespread cities from Argentina in order to include patients from all possible backgrounds.

The important and novel information provided about the disease-related economic burden is the main contribution of this study to existing literature for MS both in Argentina and the region in terms of costs in a developing country. This information is a valuable tool to make relevant and wise decisions in the field by understanding the exact behavior of the disease in the local setting and supplementary to the use of information from Europe and North America, where resource utilization as well as cost could be rather different from those observed in a developing country like Argentina[4,9].

In conclusion, the ENCOMS study provides the Argentine health care system as well as local stakeholders with important information about the economic burden of the disease in our country. Future research performed in our country as well as in other countries of the region, taking in consideration direct and indirect costs of the disease, will expand knowledge and improve management of the disease in the region in terms of this highly relevant issue.

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