EXPERT REVIEWS

Retrospective observational study of the management of multiple sclerosis patients with resistant spasticity in Spain: the '5E' study

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Background: Multiple sclerosis spasticity (MSS) is a common and disabling symptom for which a number of antispastic agents are available; however, evidence-based guidelines for optimal management are lacking. **Objective:** This retrospective observational assessment investigated the current management approach for resistant MSS in Spain. Secondary objectives were to evaluate the evolution of MSS and to estimate the social and health-related costs of managing MSS in the Spanish healthcare system. **Methods:** A retrospective analysis was performed using case records from 212 MS patients with spasticity that were resistant to ≥1 previous therapy. Data were collected over 1–3 years (mean 2.1 years), including: sociodemographics, medical history, clinical scores and all therapy/other resources consumed (e.g., rehabilitation and carers' time). Disease progression was estimated from the evolution of recorded clinical scales, and an analysis of costs from a Spanish healthcare and social perspective was performed. **Results:** The majority of patients were female and most had secondary progressive MS. Baclofen (76–80%), tizanidine and benzodiazepines were the most common antispastic drugs administered. A variety of spasticity rating scales were employed, and they demonstrated the same general trends. MS progressed, with the composite score for spasticity and mobility deteriorating in 46.4% of patients, and there were no marked differences between antispasticity drugs. The annual healthcare-related cost of treating an MSS resistant patient in the Spanish healthcare system was €15,405, largely attributable to the cost of disease-modifying drugs and care provision. Other aspects, such as medical visits and antispastic treatments, formed only a small portion of cost. **Conclusions:** MSS progresses despite treatment with currently available antispastic agents, and it is associated with a high level of disability. Spasticity treatment represents a minor element of the overall cost of managing MSS patients in Spain. The approach to the assessment of spasticity varies between centers.

Keywords: healthcare costs • multiple sclerosis • Spain • spasticity

Multiple sclerosis spasticity (MSS) is a frequent and disabling symptom of multiple sclerosis (MS), affecting approximately 80% of MS patients to some extent [1]. As experienced by the patient, it involves tightening of the muscles, cramping, spasms and movements such as bouncing of the foot, jumping of the legs, and straightening or drawing up of the limbs [1]. Spasticity has adverse effects on a range of activities, such as walking, posture maintenance and bladder function, and can lead to discomfort, difficulty sleeping and depression [1].

The clinical assessment of spasticity includes an evaluation of muscle strength, stiffness, tendon reflexes, clonus, extensor and flexor spasms, range-of-motion, co-contraction of antagonist muscles and pain [2]. Various spasticity grading scales can be used in the clinical setting. The modified Ashworth Scale is one of the most widely used [3], although a numerical rating scale (NRS) may be more sensitive and reliable [4,5]. Spasms can be evaluated using the Spasm Frequency Scale [6]. In addition, it is important to assess the effect that spasticity has on functioning and quality of life, as this

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can determine whether, and what, treatment is needed [2]. The Multiple Sclerosis Spasticity Scale can help assess the impact of spasticity on the patient, although it is time-consuming to complete [7]. In addition, any treatable precipitating factors should also be sought and managed [2].

A number of physical and pharmacological treatments are used in patients with MSS. The most common physical modalities include stretching, strengthening and mobilization techniques, including massage and dynamic physiotherapy [2,8]. In addition, muscle-cooling techniques, electrical stimulation and focal neuromuscular blocks may be beneficial to some patients. Orthosis and mobility aids may be needed to aid functioning [8].

As the disease evolves, most patients will also receive antispastic medication. Spasticity can be ameliorated by a number of classic, general antispastic drugs, although a systematic review undertaken by the Cochrane Group concluded that the overall clinical benefit of such agents was small [9]. The Multiple Sclerosis Council in the USA recommends a stepped approach to therapy, in which individual agents are tried sequentially, before proceeding to combination therapy [2]. The same guidance recommends that the selection of the agent should be tailored to the individual, and suggests that baclofen or tizanidine are generally appropriate initial options for spasticity that lasts for most of the day [2].

If it is not managed adequately, MSS can contribute to progressive disability and impaired quality of life [1,8,10]. Spasticity has been reported to adversely affect the ability to perform daily activities in up to 44% of patients with MS [10]. This, in turn, increases the need for assistance from carers.

Multiple sclerosis is a chronic disease and places a substantial financial burden on healthcare systems, social services and society [11,12]. The specific contribution of spasticity to the economic burden is not well characterized; however, it will certainly contribute to treatment- and care-related costs.

Despite the importance of treating MSS, there are few evidence-based guidelines regarding its optimal management [2]. Our group conducted a retrospective obervational assessment to determine the current management approach used for patients with resistant MSS in Spain, including usual medical treatment and supportive measures. The secondary objectives were to evaluate the clinical evolution of MSS over time, and to estimate the social and health-related costs of managing MSS patients in the Spanish healthcare system.

Methods

The primary objective was to provide a description, using a retrospective, observational approach, of the present management (usual treatment and follow-up) of patients with resistant MSS (defined as MSS requiring at least a second treatment for its relief) in Spain.

The secondary objectives were to describe patients' recorded clinical evolution, considering the therapeutic plan received for their spasticity, and to estimate the health-related costs for the management of spasticity in patients with resistant MSS.

A retrospective analysis of patient records from 11 Spanish MS centers was performed in 2009, capturing data recorded between 2006 and 2009 for patients with MS and spasticity that was resistant to at least one previous course of therapy (Figure 1). Patients were excluded if they used illicit cannabis. Data covering a period of 1–3 years of follow-up were entered into web-based case report forms. This included sociodemographic data, medical history, scores for the Extended Disability Status Scale (EDSS) [13], spasticity and other clinical scales, details of therapy for MS and MSS, and other resources consumed (such as rehabilitation, tests and carers' time).

Disease progression from baseline to study end was estimated from the evolution of clinical scales. The clinical evolution of spasticity and mobility was evaluated based on five parameters:

- Change in spasticity: NRS or categorical scale [14];
- Change in rigidity: modified Ashworth or categorical scale [3,15];
- Change in mobility: Ambulation Index [16];
- Change in spasms: Penn scale [17];
- Change in muscle weakness: Medical Research Council (MRC) or categorical scale [18].

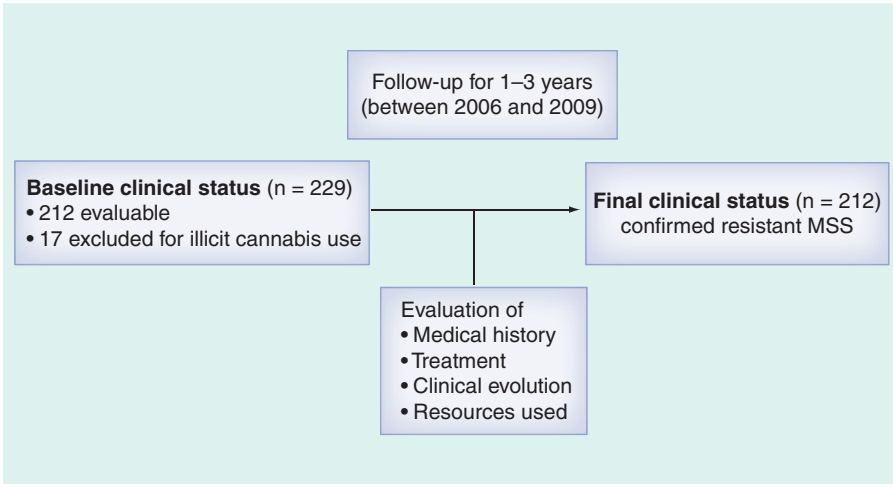

Figure 1. Study structure.
MSS: Multiple sclerosis spasticity.

Since a variety of different scales were used by the MS centers to ascertain disease severity, an approximate estimate of overall change associated with treatment was obtained by assigning scores of +1 for improvement, 0 for no change and -1 for worsening between the baseline and final visits for each parameter. The scores were added together to provide a composite score, with a positive score implying overall improvement, 0 implying no overall change and a negative score implying an overall worsening of the composite score for spasticity plus mobility.

The economic evaluation was an analysis of costs performed from a Spanish healthcare perspective, and was based on the

Table 1. The 5E study group centers and investigators, and the number of patients recruited per center in Spain.

Center	Investigators	Patients (n)
Hospital Clínico U. San Carlos, Madrid	Rafael Arroyo (study coordinator), Beatriz Parejo, Virginia de las Heras	25
Hospital del Mar, Barcelona	José E Martínez Rodríguez, María Sepúlveda Vázquez	22
H. U. Miguel Servet, Zaragoza	Jesús Martín Martínez, Berta Sebastián Torres	2
Hospital U. Puerta de Hierro, Madrid	J Antonio García Merino, Mª Rosario Blasco Quilez	30
H. Reg. U. Carlos Haya, Málaga	Oscar Fernández Fernández, Ana María Alonso Torres	25
H. U. Dr. Josep Trueta, Girona	Lluís Ramió Torrentà, Héctor Perkal	6
H. U. Virgen de la Macarena, Sevilla	Guillermo Izquierdo Ayuso	20
H. C. U. Santiago de Compostela	José Maria Prieto, José Carlos Fernández Ferro	19
Hospital de la S.C. i Sant Pau, Barcelona	Antonio Escartín Siquier, Nuria Vidal, Mariana López	20
H. U. Germans Trias i Pujol, Badalona	Cristina Ramo, Ana María Domínguez Cobo	20
H. U. Vall Hebrón (CEMCAT), Barcelona	Francisco Pérez Miralles, Xavier Montalbán	33

applicable market costs for disease-modifying drugs (DMDs) and antispastic treatments, tests (including laboratory tests, MRI scans, lumbar punctures and evoked potentials), clinic visits (hospitals, primary care and nurses), rehabilitation (including physiotherapy), the use of incontinence pads and recorded carers' time/costs. Carers included social workers, carers hired by the patient or their family, and carers within the patient's family. The year of costing was 2009, and all cost values came from publicly available Spanish sources, including an official pharmaceutical price list.

Costs per unit in the calculations came from the eSALUD (eHealth) costs database [101], which was consulted in February 2010; it provides the official Ministry of Health prices in Spain for medications plus visits, medical tests, carers and other parameters [102]. For medication cost calculations, where possible, the study recorded the medication dosage used, and, when not available, the daily defined dose for the indication was used. Examples of key costs used in the calculations include: neurologist visit: €121.50/visit; emergency visit: €138.10/visit; rehabilitation visit: €12.50/visit; basic laboratory tests: €37.00; social worker: €24.80/h; privately hired carer: €8.53/h; and family carer (state subsidy): €392.50/month.

The retrospective observational study was designed to provide exploratory and descriptive outcomes data. The study sample size was not dimensioned to be powered for between-subgroup comparisons and the protocol was not designed to reflect comparative analyses. No tentative statistical analyses were performed.

Results

Patient characteristics

The records of 229 patients were examined, of which 17 were excluded because of reported illicit cannabis use. The remaining 212 evaluable patients had a mean retrospective follow-up of 2.1 years. The number of patients recruited per center is shown in Table 1.

The characteristics of the patients at the final visit provide a profile of patients with resistant MSS in Spain (Table 2). The majority were female (63%), with an average age of 49 years and a history of MS of 14.5 years. Most patients had secondary progressive MS (53.8%), the average EDSS score was more than 6, and just over a third were wheelchair-bound or bedridden. Although the mean age was 49 years, the majority were not

Table 2. Patients' characteristics at final visit (n = 212).

Characteristic	Data
Mean age (years)	49.4 (SD ± 9.3; range: 25–68)
Mean duration of MS (years)	14.5 (SD ± 6.8; range: 1–42)
Age at MS diagnosis (years)	34.8 (SD ± 9.5; range: 15–62)
MS type	Relapsing–remitting: 26.4% Primary progressive: 19.8% Secondary progressive: 53.8%
Extended Disability Status Scale score	6.4 (SD ± 1.7)
Wheelchair-bound/bedridden	34.6%
Working status	Employed: 18% Unemployed: 3% Housewife: 9% Retired: 70%
Social support	Living alone: 1.4% Not living alone: 57.5% Status unknown: 41.0%
Disease-modifying treatment	56.6%
Spasticity rating scales recorded	Modified Ashworth: 59% Categorical scales (mild/moderate/severe): 44% Numerical Rating Scale: 16%

MS: Multiple sclerosis; SD: Standard deviation.

Table 3. Number and percentage of patients taking the various spasticity medications at baseline and at the end of treatment†.

Treatment	Baseline visit (n = 204)		Final visit (n = 209)	
	Patients (n)	*%*	*Patients (n)*	*%*
Baclofen	154	75.5	168	80.4
Tizanidine	76	37.3	84	40.2
Benzodiazepines	65	31.9	82	39.2
Gabapentin	32	15.7	35	16.7
Clonidine	0	0	0	0
Dantrolene	0	0	0	0
Botulinum toxin	26	12.7	58	27.8
Cannabis oromucosal spray	23	11.3	42	20.1
Others	9	4.4	13	6.2

†Some patients were taking more than one drug.

working, and less than 2% were living on their own. More than half of the patients were receiving DMD treatment (56.6%; see Table 2).

Management of MSS

There was considerable variation in the medications used to treat spasticity between centers and patients, and combination therapy was common. The most widely used agent was baclofen (80% of patients at the final visit), followed by tizanidine (40%), benzodiazepines (39%), botulinum toxin (28%) and cannabis oromucosal spray (20%; pre-approval use; see Table 3).

The majority of patients received more than one pharmacological intervention. Only ten out of 212 patients received monotherapy for MSS throughout the study. Of these patients, six remained stable, one improved and three worsened. The use of specific DMDs at the baseline and final visits is shown in Table 4. During the study, 56.4% of patients had stable DMD use, 35.3% of patients changed DMDs between baseline and the final visit, and 8.3% of patients received no DMDs at all.

Table 4. Disease-modifying drug use at baseline (n = 141) and final visit (n = 120).

DMD	Baseline, n (%)	Final visit, n (%)
iv./sc. corticosteroids	15 (10.6)	24 (20.0)
Oral corticosteroids	10 (7.1)	23 (19.2)
IFN-β-1a (im.)	13 (9.2)	11 (9.2)
IFN-β-1a (sc.)	40 (28.4)	31 (25.8)
IFN-β-1b	44 (31.2)	35 (29.2)
Glatiramer acetate	11 (7.8)	14 (11.7)
Natalizumab	7 (5.0)	15 (12.5)
Mitoxantrone	17 (12.1)	4 (3.3)
Other MS treatments	22 (15.6)	16 (13.3)

DMD: Disease-modifying drug; im. : Intramuscular; iv.: Intravenous; MS: Multiple sclerosis; sc.: Subcutaneous.

Nonpharmacological therapy for MSS was recorded in approximately 56% of patients, with around a third of patients receiving rehabilitation, a third physiotherapy and 20% receiving orthopedic support. However, patients had relatively few visits to healthcare facilities, with 95% of patients having two to three visits per year, and only 6% having more than three visits annually.

Evaluation of MSS

In terms of the evaluation of MSS symptoms, the most commonly used spasticity rating scale was the modified Ashworth Scale (59%); however, there was considerable variation in terms of the scales that centers preferred to use to assess spasticity/mobility (Table 2).

Clinical evolution

Multiple sclerosis tended to deteriorate over time (EDSS average changed from 6.1 to 6.4) and, in parallel, DMDs were used less (approximately 67% at retrospective baseline vs 57% at study end).

When considered together, spasticity and mobility mostly showed deterioration (46.4%) or remained unchanged (40.8%) in MSS patients, based on an evaluation of the change in overall composite evolution score between baseline and final visit (Figure 2). Despite the heterogeneity among centers in terms of the clinical scales used to assess spasticity and mobility, results for the various rating scales all demonstrated similar trends (Table 5). For example, between the baseline and final visits, the spasticity NRS score increased by 3.5%, the proportion of patients reporting severe spasticity on categorical scales increased from 42 to approximately 55%, and the proportion of patients with a modified Ashworth Scale score of three or four increased from 30 to 50% (Table 5). Likewise, the proportion of patients who were wheelchair-bound or bedridden increased from 25 to 35% (Table 5).

Deterioration in MSS occurred despite active antispastic therapy, and there was a similar general trend in the evolution of the composite score for spasticity and mobility, irrespective of which agent was used (Table 6).

Economic analysis

Based on the data collected for this study, the average healthcare-related annual cost of treating an MSS patient in Spain was €15,405 (2009 costs; Figure 3). This sum was largely made up of the costs of DMDs (56%) and recorded carer costs (36%). Antispastic drug therapy (including a small number of patients treated with an oromucosal cannabis spray; pre-approval use) represented only 5% of the costs. The combined costs for tests, clinic visits, rehabilitation and incontinence pads use accounted for only a small portion (3%) of the healthcare-related costs for Spanish MSS patients. Indeed, the number of rehabilitation/physiotherapy visits recorded in the case report forms was very low (120 visits/all patients/2.1 years). Furthermore, the cost per visit in Spain is low.

Discussion

Spasticity is a common feature of MS, and contributes to reduced mobility and impaired quality of life [1,10]. A third of MS patients have to alter or stop normal daily activities because of spasticity [1]. Consequently, as the disease progresses, many MS patients need assistance with personal care and other daily activities. This necessitates the involvement of a caregiver, either organized by healthcare or social services or, commonly, through the informal care provided by family members [19].

The treatment of spasticity is important in order to limit its contribution to progressive disability over the long term [1,2,8,10]. The most widely used oral antispastic agent is baclofen, while other commonly used agents include tizanidine, dantrolene, benzodiazepines and gabapentin [8,20] These antispastic drugs can improve spasticity symptoms, but they may be of limited benefit in terms of functional improvements, particularly in patients with resistant MSS [9,20]. Furthermore, tolerability issues (most notably muscle weakness, drowsiness and liver toxicity) restrict their potential, and more effective treatments are required [9].

With few evidence-based guidelines available for the management of MSS [2], there may be variations between different treatment centers in terms of how the condition is assessed and treated. The current study evaluated the characteristics of patients with resistant MSS and the treatment approaches employed in the management of this patient population in Spain.

Our study confirms that patients with resistant MSS have a long disease evolution and a high level of associated disability. Clinical status tended to worsen progressively (all disease evolution

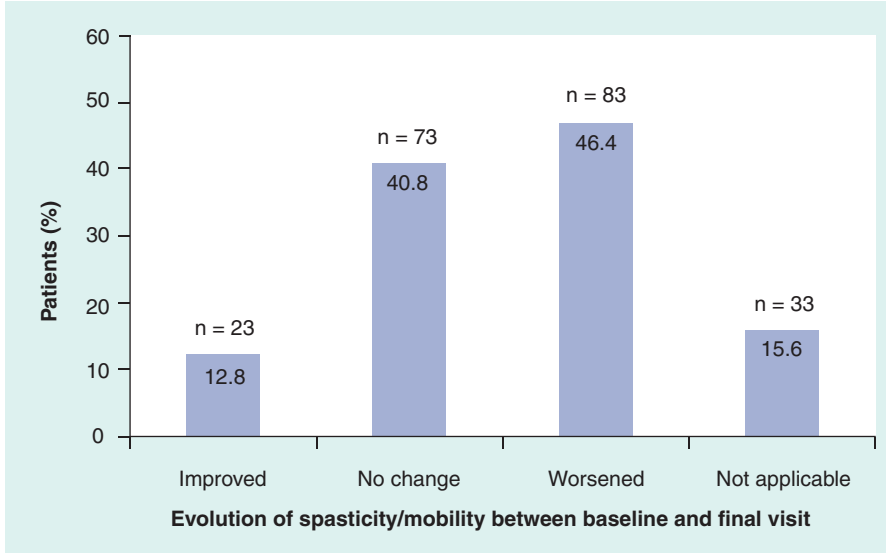

Figure 2. Evolution of spasticity and mobility in multiple sclerosis spasticity patients: overall composite evolution score based on spasticity and mobility rating scale scores at baseline and final visit.

Table 5. Evolution of spasticity/mobility in multiple sclerosis spasticity patients based on individual spasticity rating scale scores at baseline and at final visit.

Evaluation	Baseline visit (n = 198)	Final visit	MSS evolution (%)
Disability evaluation			
	n = 198	n = 204	
Mean EDSS scale value (SD)	6.1 (1.7)	6.4 (1.7)	+4.9
Spasticity severity			
	n = 31	n = 37	
Mean NRS scale value (0–10) (SD)	5.7 (1.9)	5.9 (2.1)	
Other spasticity evaluations, n (%)	n = 81	n = 99	
Mild	7 (8.6)	3 (3.0)	+3.5
Moderate	39 (48.1)	42 (42.4)	-5.6
Severe	34 (42.0)	54 (54.5)	-5.7
N/A	1 (1.2)	0 (0.0)	+12.5
Muscle rigidity			
Modified Ashworth Scale value, n (%)	n = 104	n = 39	
1	10 (9.6)	15 (10.8)	+1.25
1+	26 (25.0)	18 (12.9)	-12.1
2	37 (35.6)	37 (26.6)	-9.0
3	24 (23.1)	56 (40.3)	+17.2
4	7 (6.7)	13 (9.4)	+2.7

EDSS: Extended Disability Status Scale; MRC: Medical Research Council; MSS: Multiple sclerosis spasticity; N/A: Not available; NRS: Numerical Rating Scale; SD: Standard deviation.

Table 5. Evolution of spasticity/mobility in multiple sclerosis spasticity patients based on individual spasticity rating scale scores at baseline and at final visit.

Evaluation	Baseline visit (n = 198)	Final visit	MSS evolution (%)
Muscle rigidity (cont.)			
Other muscle rigidity evaluations, n (%)	n = 41	n = 56	
Mild	3 (7.3)	2 (3.6)	-3.7
Moderate	23 (56.1)	24 (42.9)	-13.2
Severe	15 (36.6)	30 (53.6)	+17.0
Mobility			
Ambulation Index, n (%)	n = 158	n = 162	
No limitations	12 (7.6)	10 (6.2)	
Walks without help (≥300–500 m)	14 (8.9)	12 (7.4)	
Walks with help (≥100 m)	13 (8.2)	9 (5.6)	
Walks with help (≥50 m)	46 (29.1)	39 (24.1)	
Walks with help (<5 m)	33 (20.9)	36 (22.2)	
Wheelchair or bedridden	40 (25.3)	56 (34.6)	+9.3%
Spasm frequency			
Penn Scale value, n (%)	n = 66	n = 74	
No spasms	20 (30.3)	21 (28.4)	Similar/slightly worse
Spasms only after stimuli	28 (42.4)	30 (40.5)	Similar/slightly worse
Spontaneous spasms <once per h	16 (24.2)	19 (25.7)	Similar/slightly worse
Spontaneous spasms >once per h	2 (3.0)	4 (5.4)	Similar/slightly worse
Spontaneous spasms >10 times per h	0 (0.0)	0 (0.0)	Similar/slightly worse
Muscle weakness			
MRC Scale value, n (%)	n = 144	n = 169	
(0) Absent (total paralysis)	4 (2.8)	8 (4.7)	+1.9%
(1) Minimal: visible muscle contraction without movement	9 (6.3)	25 (14.8)	+8.5%
(2) Scarce: movement in absence of gravity	29 (20.1)	36 (21.3)	+1.2%
(3) Regular: partial movement against gravity	39 (27.1)	38 (22.5)	-4.6%
(3+) Regular+: full movement against gravity	11 (7.6)	16 (9.5)	+1.9%
(4-) Good-: full movement against gravity, minimal	33 (22.9)	33 (19.5)	-3.4%
(4+) Good+: full movement against gravity, strong	18 (12.5)	12 (7.1)	-5.4%
(5) Normal: full movement against full resistance	1 (0.7)	1 (0.6)	-0.1%
Other motricity evaluations, n (%)	n = 14	n = 23	
Mild	1 (7.1)	2 (8.7)	
Moderate	2 (14.3)	3 (13.0)	
Severe	11 (78.6)	18 (78.3)	

EDSS: Extended Disability Status Scale; MRC: Medical Research Council; MSS: Multiple sclerosis spasticity; N/A: Not available; NRS: Numerical Rating Scale; SD: Standard deviation.

parameters worsened). In addition, spasticity tended to worsen despite treatment with a variety of antispastic drugs, often used in combination. Although the study protocol did not allow for the capture of specific reasons for MSS medication failure, spasticity evolution could not be prevented in approximately half of all patients. There was no evidence of substantial clinical differences between the available agents in terms of their effect on spasticity evolution in this patient population. Across individual agents, 40–60% of patients experienced worsening of their spasticity/mobility regardless of treatment. Clearly there is a need for improved therapeutic options for this difficult-to-treat group of patients with resistance to at least one previous antispastic therapy.

Our study also included an evaluation of the spasticity rating scales used at each center. A number of different clinical rating scales are available for use in the assessment of patients with MSS. The modified Ashworth Scale is widely used to assess the severity of spasticity, and indeed was the most commonly applied instrument in our study, reported by 59% of centers [3]. However, a number of studies have demonstrated that it lacks validity and reliability [5,21]. In addition, it involves the physician's assessment of the stiffness of certain muscles at one time point during the day, which may not reflect the patient's overall experience [5]. By contrast, the spasticity NRS records the patient's impression of spasticity severity over a whole day, and

Table 6. Evolution of a composite score for spasticity and mobility between baseline and final visit according to patients' antispastic treatment.

Treatment	Spasticity/mobility: improved (% patients)	Mean treatment duration (months)	Spasticity/mobility: no change (% patients)	Mean treatment duration (months)	Spasticity/mobility: worsened (% patients)	Mean treatment duration (months)
Baclofen	13.9 (n = 21)	25.8	39.1 (n = 59)	23.4	47.0 (n = 71)	24.6
Tizanidine	12.5 (n = 11)	27.6	34.1 (n = 30)	21.9	53.4 (n = 47)	23.6
Benzodiazepines	16.4 (n = 11)	24.7	26.0 (n = 18)	20.6	56.7 (n = 14)	22.9
Gabapentin	14.3 (n = 5)	22.9	45.7 (n = 16)	21.2	40.0 (n = 14)	21.3
Clonidine	N/A (n = 0)	N/A	N/A (n = 0)	N/A	N/A (n = 0)	N/A
Dantrolene	N/A (n = 0)	N/A	N/A (n = 0)	N/A	N/A (n = 0)	N/A
Botulinum toxin	10.3 (n = 6)	17.2	44.8 (n = 26)	9.2	44.8 (n = 26)	21.3
Cannabis oromucosal spray	12.3 (n = 7)	9.1	36.8 (n = 21)	7.3	50.9 (n = 29)	13.5
Others			33.3 (n = 6)	10.6	61.1 (n = 11)	6.6

N/A: Not available.

there is evidence that it is more reliable and sensitive than the modified Ashworth Scale [5,14]. Interestingly, in our study, the NRS was only used by 16% of centers. Aside from the modified Ashworth Scale and NRS, more than 40% of the centers in our study used categorical scales (mild/moderate/severe) to assess spasticity. Thus, at present, there appears to be substantial variation among Spanish MS centers in terms of preferred rating scales. This is an area worthy of more research, as the consistent use of reliable, sensitive scales could help in the evaluation of new treatment strategies.

The management of MS is associated with a substantial financial burden for healthcare systems and for society. A review of 32 cost-of-illness studies in MS, which took either a healthcare or societal perspective, found that the annual cost per patient ranged from approximately US$6500 to 78,000 (2008 values) [11]. A study across nine European countries estimated that the total mean annual cost from a societal perspective was €18,000 per patient with mild MS, rising to €62,000 per patient with severe disease (2005 values) [12]. Generally, around half of the total cost was borne by healthcare systems and social services, with the remainder accounted for by costs outside the healthcare system, such as informal care by family members and lost work productivity [12]. In addition, MS is associated with intangible costs related to pain, emotional distress, social handicap and the patient's changed health status. A Spanish study estimated these intangible costs to be between €1100 and 11,000 per patient per year, depending on the level of disability [22].

Our study specifically evaluated the cost of managing MS patients who had resistant spasticity from a Spanish healthcare perspective. On this basis, the healthcare-related cost of managing resistant MSS was approximately €15,400 per patient per year (2009 values). The actual cost may be higher than this, since it is possible that not all carer-related costs and other indirect costs were captured in the patients' center records. Nonetheless, care provision accounted for more than a third of the total cost in the current study. In terms of direct medical costs, the biggest contributor was DMD treatment, which accounted for more than half of the healthcare-related cost. Medical visits and rehabilitation costs formed only a very small portion of the healthcare-related cost (3%), highlighting potential

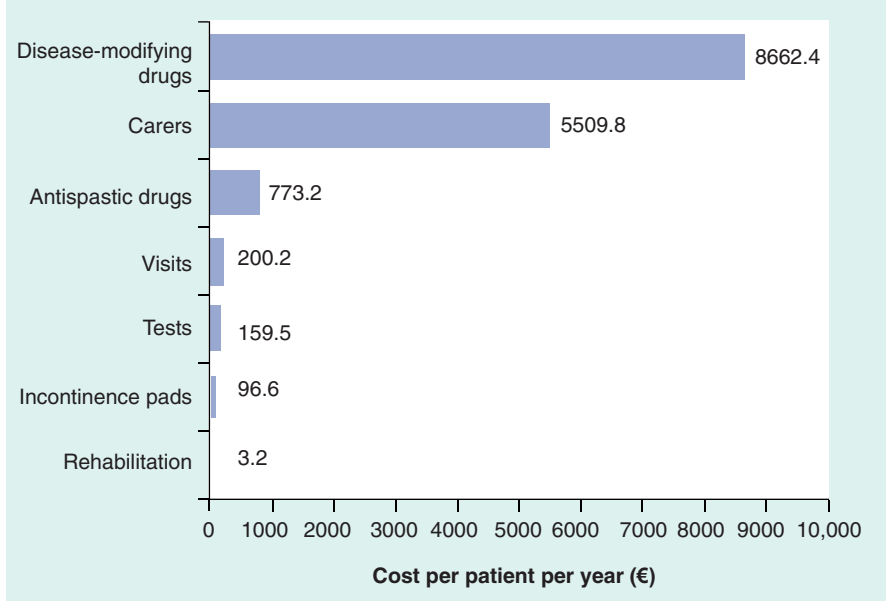

Figure 3. Management costs for multiple sclerosis spasticity patients in Spain (€/patient/year).

areas for improved management. Likewise, antispastic treatments also represented a small part (5%) of the healthcare-related cost of managing resistant MSS patients in Spain.

In conclusion, this retrospective observational study of patients with resistant MSS confirms that MSS progresses despite treatment with a variety of antispastic agents, and that it is associated with a high level of disability. Spasticity treatments represent a minor part of the overall cost of managing MSS patients in Spain. Finally, the approach to the assessment of spasticity varies between centers.

Expert commentary & five-year view

Multiple sclerosis is a distressing and debilitating disease, which often leads to a state of progressive deterioration for the individual. Throughout this progression, spasticity is a frequent and disabling neurological feature and its relief becomes a key component of the day-to-day care process for MS patients. The management of MSS includes a range of options from exercise programs (including stretching and relaxation techniques), pharmacotherapy (for MS, spasticity and related symptoms such as urinary incontinence) and day-to-day care. MS patients become less able to look after themselves over time, and friends or family generally have to help provide some care and/or hire some additional assistance, which can be physically and financially demanding. Indeed, the cost of managing MS and the consequences of MS spasticity can be substantial. For example, in our study involving Spanish patients with resistant MSS, we found that the cost of managing a patient was more than €15,000 per year. However, the costs of DMDs accounted for more than half of the costs of treatment, while antispastic therapy was responsible for only 5% of the total costs. Care provision accounted for 36% of the overall cost.

Current treatments for MSS have been demonstrated to produce some symptomatic relief but, overall, they are of limited benefit, particularly in terms of improving functionality and wellbeing. Patients worsen or remain stable, which can also be a goal itself, as MS evolves. This is an important area for future clinical research since spasticity is a major cause of disability, and this is associated with increased costs that are needed to provide treatment, and, more relevantly, assistance and personal care. Consequently, more effective treatments will not only improve the patient's quality of life and wellbeing, they will also reduce the financial burden on healthcare and social care systems. In recent years, there has been increasing medical interest in the role of the endocannabinoid system in health and disease. For example, there is evidence that the cannabinoid CB_1 receptor plays a role in modulating spasticity in MS [23]. Initial experience with the endocannabinoid modulator Sativex® (GW Pharma, Porton Down, UK) has produced some encouraging results and it has recently been approved for the treatment of MS-related spasticity in Canada, Spain and the UK. Clinical experience with Sativex in patients with MS has been accumulating steadily and the results from randomized controlled trials to date have reported a reduction in the severity of symptoms associated with spasticity, leading to a better ability to perform daily activities and an improved perception of patients and their carers in terms of functional status [24]. While these findings regarding improved functional status are promising, they need to be confirmed in large long-term follow-up studies.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Financial & competing interests disclosure

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Key issues

- Spasticity is a common symptom in multiple sclerosis and can lead to considerable disability.
- A number of antispastic agents are used to treat multiple sclerosis spasticity (MSS), but evidence-based guidelines on its optimal management are lacking.
- The aims of this retrospective observational assessment were to determine the current management approach for patients with resistant MSS in Spain, to evaluate the clinical evolution of MSS and to estimate the health-related costs of managing MSS patients in the Spanish healthcare system.
- The most commonly used antispastic agents were baclofen, tizanidine and benzodiazepines. Overall, there were no marked differences between antispastic drugs with regard to their effect on MSS evolution.
- The rating scales used to assess spasticity varied between centers, although individual scales demonstrated the same general trends.
- MSS progressed (or remained unchanged) in most patients, despite treatment with disease-modifying drugs and a variety of antispastic drugs.
- In terms of the annual cost for treating an MSS patient, the largest cost contributors were disease-modifying drugs and care provision. Antispastic drugs and other management costs represented only a small portion of the total cost.

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