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# Spasticity treatment patterns among people with multiple sclerosis: a Swedish cohort study

Kelsi A Smith <sup>1</sup>, Fredrik Piehl<sup>2,3,4</sup>, Tomas Olsson<sup>2,3,4</sup>, Lars Alfredsson<sup>2,3,5</sup>, Jan Hillert <sup>2,3</sup>, Ingrid Kockum<sup>2,6</sup>, Pernilla Stridh<sup>2,6</sup>, Scott Montgomery<sup>1,7,8</sup>

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<sup>1</sup>Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institute, Stockholm, Sweden

<sup>2</sup>Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

<sup>3</sup>Centre of Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden

<sup>4</sup>Academic Specialist Centre, Centre of Neurology, SLSO, Stockholm, Sweden

<sup>5</sup>Centre of Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden

<sup>6</sup>Centre for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden

<sup>7</sup>Clinical Epidemiology and Biostatistics, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

<sup>8</sup>Department of Epidemiology and Public Health, University College London, London, UK

## Correspondence to

Kelsi A Smith, Department of Medicine Solna, Karolinska Institute, Stockholm, Sweden; [kelsi.smith@ki.se](mailto:kelsi.smith@ki.se)

PS and SM are joint last authors.

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## ABSTRACT

**Background** Spasticity is common among people with multiple sclerosis (MS), but there are few studies of spasticity treatment patterns. We aim to describe associations with spasticity treatment measured primarily by oral baclofen use.

**Methods** This cohort study using Swedish registers included 1826 and 3519 people with incident and prevalent MS (pwIMS, pwPMS) respectively, followed from 2005 to 2014. Cox regression assessed factors associated with new baclofen prescriptions and its discontinuation.

**Results** A total of 10% of pwIMS and 19% of pwPMS received baclofen, a drug prescribed specifically for spasticity in Sweden, of which many patients had relapsing-remitting course. Prescriptions occurred soon after MS diagnosis: pwIMS received baclofen typically within 6 months of diagnosis, and pwPMS within 3 years. Younger patients compared with older patients were three times more likely to receive baclofen with similar disability level measured using Expanded Disability Severity Scores (EDSS). Patients aged 18–44 years with EDSS 3.0–5.0 have an HR for baclofen use of 5.62 (95% CI 2.91 to 10.85) and EDSS 6+ have an HR of 15.41 (95% CI 7.07 to 33.58) compared with individuals with EDSS 0–2.5. In comparison, patients aged 45+ years with EDSS 3.0–5.0 have an HR of 2.05 (95% CI 1.10 to 3.82) and EDSS 6+ an HR of 4.26 (95% CI 1.96 to 9.17). Baclofen discontinuation was high: 49% (95% CI 0.42 to 0.57) of pwIMS discontinued within 150 days of dispensation, 90% discontinued within 2 years including patients with progressive course or higher EDSS. Associations among pwPMS and sensitivity analyses including additional treatments were similar.

**Conclusions** Younger patients with MS are more likely to receive baclofen compared with older patients with MS. High rates of baclofen discontinuation highlight the need for more tolerable and efficacious spasticity treatments and monitoring of spasticity among people with MS.

## INTRODUCTION

Spasticity is a result of changes in muscular stretch reflexes<sup>1</sup> and is a complication of multiple sclerosis (MS) possibly reflecting disease severity and progression, or individual susceptibility. Cross-sectional, register-based studies of individuals with prevalent MS in Germany and North America report spasticity prevalence between 53%<sup>2</sup> and 60%<sup>3</sup> to greater than 80%<sup>4</sup> of varying severity, with increases in spasticity severity associated with a progressive MS

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies of spasticity among people with multiple sclerosis (MS) are few. Factors increasing the need for spasticity treatment are largely unknown given the impact of spasticity in the day-to-day lives of people with MS.

## WHAT THIS STUDY ADDS

⇒ This is the first large, population-based assessment of spasticity treatment following patients over 10 years and shows that younger, newly diagnosed people with MS are prescribed baclofen to treat spasticity, especially those with greater disability compared with older patients with MS. This is the first study to show high rates of baclofen discontinuation among all patients with MS as more than half stopped treatment within 6 months.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Spasticity may occur earlier among patients with MS than previously thought, which is of importance for treating clinicians managing MS symptoms. High rates of baclofen discontinuation demonstrates a low success rate of treating spasticity and demonstrates an unmet need of tolerated, effective spasticity treatments. This study provides evidence for the timing of treatment, and highlight issues with long-term treatment using baclofen to manage spasticity.

disease course.<sup>3,4</sup> Spasticity can present with a range of symptoms even among individuals with a similar level of functioning.<sup>4,5</sup> Variation in levels of severity can occur even over a short period of time and spasticity is present commonly in the lower extremities among people with MS (pwMS).<sup>4,6,7</sup> Spasticity has an impact on many aspects of an individual's life including quality of life, mobility,<sup>3</sup> pain<sup>8</sup> and leads to increased disability.<sup>4</sup>

The specific pathophysiology of spasticity among pwMS is unknown. One hypothesis postulates spasticity is due to lesions in upper motor neuron pathways in the central nervous system. This causes increases in muscular reflex stretches and muscle tone similar to spasticity observed among diseases involving upper motor neuron syndromes.<sup>1,7</sup> Treatments for spasticity vary by country, often involving a multidisciplinary approach.<sup>9</sup> Oral baclofen is the

only approved first-line pharmacological treatment for spasticity in Sweden, while the cannabinoid Sativex is approved for moderate to severe spasticity with insufficient response to other lines of therapy. As Sativex is not reimbursed in Sweden, its use is very limited. Baclofen can be delivered in tablet form or intrathecally, although intrathecal baclofen pumps are reserved as a second-line treatment for severe spasticity. Certain other oral drug therapies are used off-label to treat spasticity, including diazepam, clonazepam and gabapentin.<sup>10</sup> More rarely used drug therapies include tizanidine, dantrolene or botulinum toxin A injections.<sup>10</sup>

Studies of spasticity among pwMS are rare and mostly involved patients with prevalent MS using a cross-sectional study design, assess spasticity using self-reported data or were clinical trials. Studies using self-assessed spasticity among patients with prevalent MS found that most often spasticity affects males, individuals with progressive forms of MS, and older individuals.<sup>4-6</sup> Conditions such as seizures and stroke are associated with spasticity among people with prevalent MS.<sup>4-6</sup> Disease-modifying therapies (DMTs) and their effects on spasticity are not well studied, although beta-interferon may exacerbate spasticity.<sup>7</sup> Clinical guidelines are often based on clinical-trial data, and there is no comprehensive study of treatment patterns using objective measures among a wide-range of patients with MS in the real-world context. Understanding how and why spasticity manifests frequently among pwMS will help identify possible preventative strategies and earlier treatment possibilities. Our aim was to determine associations with a proxy measure of spasticity, use of oral baclofen among people with incident and prevalent MS (pwIMS, pwPMS) diagnoses using Swedish national registers.

**METHODS**

**Study setting and population**

The follow-up for this cohort study was from 1 July 2005 to 31 December 2014 and linked data from Swedish registers to

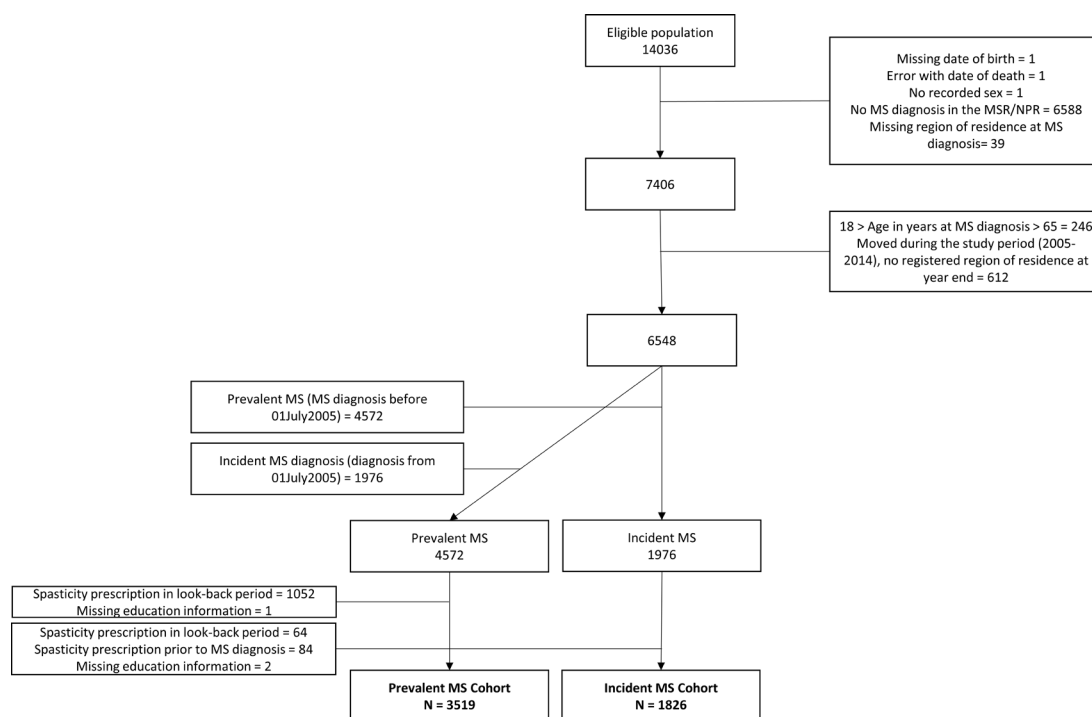
epidemiological case-control studies of MS in Sweden: the Epidemiological Investigation of MS (EIMS), Genes and Environment in MS (GEMS), and Immunomodulation and MS Study (IMSE) described elsewhere.<sup>11</sup>

The study population comprised pwMS consenting to participation in EIMS, GEMS or IMSE between 2004 and 2014 that were genotyped. A person was identified as having MS if they had any record in the Swedish Multiple Sclerosis Register (SMSReg) (a register containing information for 85% of the MS population recording MS-specific clinical variables since 1996<sup>12</sup>), or if they had two or more International Classification of Disease (ICD)-10 codes for MS (G35.0, G35.9) at least 180 days apart in the National Patient Register (NPR). This NPR definition has good positive predictive value when compared with the SMSReg<sup>13-15</sup> and the SMSReg has a high level of diagnostic specificity.<sup>12</sup> Previously identified controls fulfilling MS criteria were included as pwMS. Where an MS diagnosis was recorded in both the SMSReg and NPR, the earliest diagnosis date was used. If diagnosis date was missing, onset date from the SMSReg was used. Individuals diagnosed with MS between 18 and 65 years of age were included. Additional inclusion/exclusion criteria are described in figure 1.

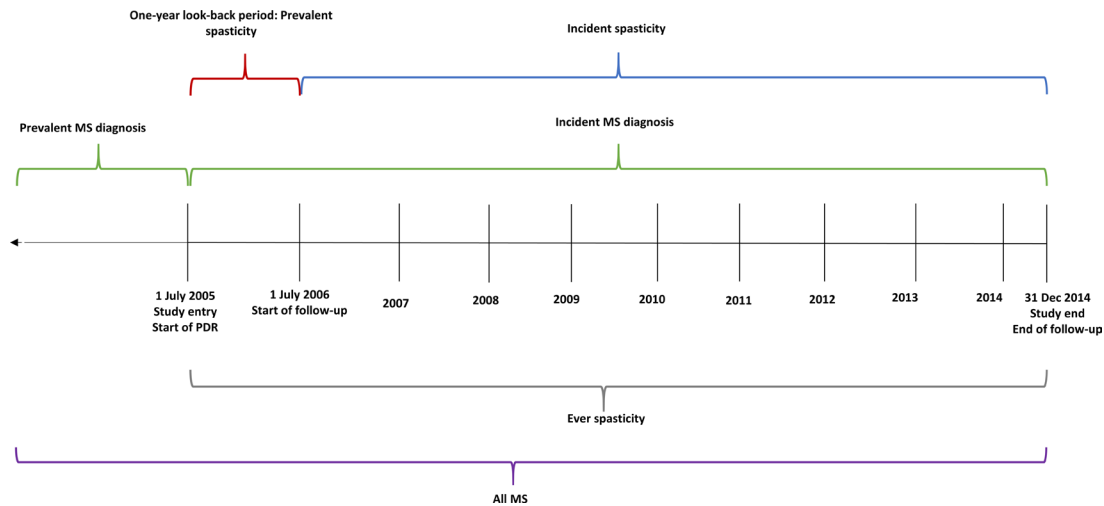
Two cohorts were defined: pwPMS and pwIMS. People diagnosed prior to 1 July 2005 were considered as pwPMS, and after 1 July 2005 were considered as pwIMS (figure 2).

**Outcome**

Dispensed medications from all pharmacies in Sweden are recorded in the Prescribed Drug Register (PDR) which started from 1 July 2005.<sup>16</sup> Date of first baclofen dispensation in the PDR from 1 July 2005 to 31 December 2014 was identified using Anatomical Therapeutic Chemical (ATC) code M03BX01. Individuals with possible spasticity treatments before MS diagnosis were excluded [ATC codes: baclofen (M03BX01), diazepam (N05BA1), clonazepam (N03AE01), gabapentin (N03AX12) or



**Figure 1** Participant flow chart for the prevalent and incident multiple sclerosis (MS) cohorts. Errors with date of death are due to reassignment of personal numbers to another person after death of an individual. MSR, Multiple Sclerosis Register, NPR, National Patient Register.



**Figure 2** Graphical depiction of how cohort populations and spasticity treatment definitions were defined. Study entry and study end is the same among both prevalent and incident multiple sclerosis (MS) diagnoses. The start of follow-up from 1 July 2006 is only applicable to people with prevalent and incident multiple sclerosis who do not have a spasticity treatment recorded in the 1-year look-back period (1 July 2005–30 June 2006). Start of follow-up for people with incident multiple sclerosis began from their multiple sclerosis diagnosis date. PDR, Prescribed Drug Register.

cannabinoids [N02BG10]). A 1-year look-back period from 1 July 2006 to 1 July 2005 was used to exclude individuals with prevalent spasticity treatments as defined above (figure 2) to account for delay of prescriptions being recorded nationally, or to allow individuals with a prior prescription to refill.

All possible spasticity treatments (all drugs named above) within the same time-period and using the same exclusion criteria as defined above, although less specific for spasticity, were also considered. This secondary outcome was defined as the date of first of any possible spasticity treatment.

### MS variables

Individuals were categorised as relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS, including primary relapsing) at the start of follow-up (1 July 2006). Individuals with a missing year of diagnosis change were considered to have SPMS from study entry and date of diagnosis change was the midpoint of the year when they were registered as SPMS (15 June).

DMTs considered as highly effective were: alemtuzumab, cyclosporin, cladribine, daclizumab, dimethyl-fumarate, fingolimod, natalizumab, ofatumumab, rituximab and teriflunomide (although not all were used in this cohort). Moderately effective DMTs were interferons and glatiramer acetate. Date of first DMT use was the earliest recorded treatment date.

Relapse dates were extracted and records with missing/erroneous dates (ie, dates before birth date), or dates 3 years prior to MS onset were excluded. Relapses within 14 days of one another were considered the same episode.

Expanded Disability Severity Scale (EDSS) scores and date of changes were categorised as 0–2.5, 3.0–5.5 and 6+ due to the large number of score changes. Baseline EDSS was defined as the score closest in time to start of follow-up, provided it was not greater than 90 days after start of follow-up.

### Potential risk factors

Diseases associated with spasticity among pwPMS were identified prior to baclofen initiation using the NPR (1 January 1997 to study-end) using ICD-10 codes and/or the PDR (from 1 July

2005 to study-end) using ATC codes further described in online supplemental table 0.

### Other variables

Highest-ever attained education was determined from LISA<sup>17</sup> and categorised as compulsory, postcompulsory and tertiary. Using the Total Population Register,<sup>18</sup> birth date was estimated as the midpoint of the month of birth (15th day), and region of residence at MS diagnosis was determined.

### Statistical analysis

#### Time to event

Follow-up for pwIMS started from MS diagnosis date and pwPMS from 1 July 2006. End of follow-up was 31 December 2014, death (identified from the Cause of Death Register<sup>19</sup>), or date of first baclofen initiation (primary outcome), whichever came first. Cox regression models used age as the underlying timescale and provided HRs for baclofen initiation. Models were adjusted for region of residence at MS diagnosis, education and other variables. Time from MS diagnosis was used as a secondary timescale. Disease course, DMTs and EDSS were used as time-varying variables and analyses including these variables were restricted to individuals with complete information. Proportional hazards were assessed using Schoenfeld residuals or with an interaction by timescale. Variables with non-proportional hazards were included using either Stratified Cox regression models, or with an interaction with the underlying timescale.

#### Sensitivity analyses

Further Cox regression models were used to examine associations with: first treatment among all possible spasticity treatments (secondary outcome); secondary outcome excluding individuals with depression and secondary outcome excluding individuals with seizures. These exclusions were conducted as the primary indication of spasticity treatments other than baclofen are seizure/epilepsy or neuropathic pain.

### Discontinuation

Time to discontinuation of spasticity treatment was assessed using failure functions for primary and secondary outcomes. For secondary outcomes, individual drugs were stratified due to differences in prescription patterns. Follow-up began from the first day of treatment dispensation until discontinuation of treatment, death or study end. Discontinuation was defined as no additional dispensation within the time from first dispensation plus gap days of possible treatment durations (90, 150 or 180 days) to account for prescribing variation for different drugs.

Data management was performed using SAS V.9.4<sup>20</sup> and analysis using STATA V.16.<sup>21</sup>

### RESULTS

Some 1826 and 3519 pwIMS and pwPMS were included and were mainly females (table 1). pwPMS were generally older, had more severe MS, had more comorbid diseases and used a greater proportion of moderately effective DMTs than pwIMS.

Median follow-up among pwIMS and pwPMS was 6.4 years (IQR= 4.5–7.9) and 8.5 years (IQR 8.5–8.5) respectively, with a median attained age of 45.5 years (IQR=37.7–53.0) and 55.7 years (IQR=48.2–64.4), respectively. Some 10.3% (95% CI 8.90% to 11.7%; n=188) of pwIMS received baclofen compared with 17.8% (95% CI 16.5% to 19.0%; n=628) of pwPMS. pwIMS and pwPMS who received baclofen were older at MS onset and diagnosis compared with those without baclofen. Most prescriptions occurred in recent calendar years, and within 6 months of MS diagnosis among pwIMS, and within 3 years of MS diagnosis among pwPMS. Approximately 30% of pwIMS and pwPMS received baclofen with an EDSS of 0–2.5. Incidence rate of baclofen initiation over the study period was 18 per 1000 people (95% CI 15.61 to 20.78) among pwIMS and 24 per 1000 (95% CI 21.70 to 25.37) among pwPMS.

### General risk factors

Among pwIMS, sex was associated with baclofen in all models (females compared with males HR 0.75 (95% CI 0.55 to 1.02)) (table 2). Disease course was strongly associated with baclofen, as progressive disease course had larger HRs compared with RRMS, even after adjustment for length of time with MS (PPMS HR 6.92, 95% CI 4.52 to 10.60; SPMS HR 5.57, 95% CI 3.82 to 8.13). A trend was seen with decreasing HRs with increasing MS time. No clear trend with year of MS diagnosis was observed, but HRs were elevated in all time periods. Age at MS onset showed no association.

Similar trends were observed among pwPMS as above (table 3). Associations with disease course, though elevated among progressive patients, were of lower magnitude after adjustment for MS time than among pwIMS (PPMS HR 5.54, 95% CI 4.22 to 7.28; SPMS HR 4.40, 95% CI 3.60 to 5.38). Age at MS onset had a small magnitude effect (HR 1.01, 95% CI 1.00 to 1.02).

### Clinical MS variables

Among pwIMS, EDSS at baseline was associated with baclofen treatment, with increasing HRs with increasing EDSS (table 4, panel A). After controlling for other MS characteristics the associations remained: EDSS 3.0–5.5, HR 3.05, 95% CI 1.61 to 5.76; EDSS 6+, HR 2.74, 95% CI 0.51 to 14.65. At MS diagnosis, both disease course and EDSS were strong predictors of baclofen initiation, although EDSS was the stronger predictor. However, when EDSS was allowed to vary over time, age-specific patterns emerged with larger magnitude HRs especially among younger

pwIMS (table 4, panel B). Individuals aged 18–44 years with EDSS 3.0–5.5 compared with same-aged individuals with EDSS 0–2.5 had an HR of 5.62 (95% CI 2.91 to 10.85). HRs increased with increasing disability: EDSS 6+, HR 15.41, 95% CI 7.07 to 33.58 even after controlling for time with MS, DMTs and disease course. At ages 45–73 years people with EDSS 3.0–5.5 or 6+ compared with EDSS 0–2.5, HRs were still elevated, but much smaller in magnitude (HR 2.05, 95% CI 1.10 to 3.82; HR 4.26, 95% CI 1.96 to 9.17, respectively). Thus, individuals with the same EDSS score, but at different ages had differences in the magnitude of the association with baclofen initiation, irrespective of when EDSS was measured. Sex differences observed in general models disappeared in these analyses when controlling for MS-specific characteristics. DMTs showed increased HRs, although few individuals used highly effective DMTs.

Relapses showed no association with baclofen initiation among relapsing-remitting pwIMS (online supplemental table 2).

Similar HRs were observed among pwPMS for EDSS at baseline, but the magnitudes of the associations with baclofen initiation were somewhat reduced (table 5, panel A). EDSS as a time-varying covariate also showed age-specific associations as seen among the incident MS cohort, and EDSS had higher magnitude associations than disease course to baclofen initiation (table 5, panel B).

### Sensitivity analyses

Widening the definition of spasticity treatments (secondary outcome) showed that baclofen and gabapentin were the most commonly prescribed (online supplemental table 1). Similar treatment patterns were found as in the main analyses among both pwIMS and pwPMS, but the magnitude of all associations reduced, especially for general characteristics (online supplemental tables 3 and 4) and EDSS scores (online supplemental table 9). Increased HRs were observed even at low EDSS values (0–3.0) as compared with no EDSS score. No association with sex was observed. After further excluding pwIMS or pwPMS diagnosed with seizures (online supplemental tables 5 and 7) or individuals treated/diagnosed with depression (online supplemental tables 6 and 8) the results were similar to the main analysis although with somewhat reduced HRs.

### Comorbid diseases as risk factors

Associations of comorbid diseases with baclofen initiation as a primary outcome could not be determined due to small numbers, but were assessed using the secondary outcome. All associations (except with depression) should be interpreted with caution due to small numbers and wide confidence intervals. In general, a diagnosis/being treated for a comorbid disease among both pwIMS and pwPMS showed increased HRs for all possible spasticity treatments, though the majority of HRs were of larger magnitude among pwIMS (online supplemental table 10). Depression, seizures and Parkinson's disease had the largest magnitude HRs. Stroke showed no association among pwIMS, but risk factors for stroke (vascular disease and coronary artery disease) had increased HRs for baclofen initiation. Among pwPMS, seizures, depression and concussion had increased HRs for baclofen initiation.

### Baclofen discontinuation

Discontinuation rates of baclofen among pwIMS (figure 3) and pwPMS (online supplemental figure 1) were similar and showed that irrespective of the gap period used (90, 150 or 180 days), 50% of individuals discontinued rapidly and 90%



**Table 1** Baseline characteristics assessed at study entry among incident and prevalent MS individuals, stratified by baclofen treatment status

Baseline characteristics	Incident MS N=1826		Prevalent MS N=3519	
	No Baclofen	Baclofen	No Baclofen	Baclofen
N (%)	1638	188 (10.29)	2891	628 (17.84)
Sex (%)				
Male	437 (26.68)	72 (38.30)	695 (24.04)	207 (32.96)
Female	1201 (73.32)	116 (61.70)	2196 (75.96)	421 (67.04)
Highest attained education (%)				
Primary education	132 (8.06)	21 (11.17)	364 (12.59)	98 (15.61)
Secondary education	767 (46.83)	97 (51.60)	1341 (46.39)	280 (44.59)
Tertiary education	739 (45.12)	70 (37.23)	1186 (41.02)	250 (39.81)
Comorbid diseases (%)*				
Depression	290 (17.70)	44 (23.40)	682 (23.59)	198 (31.53)
Concussion or TBI	3 (0.18)	0 (0.00)	8 (0.28)	0 (0.00)
Coronary artery disease	2 (0.12)	0 (0.00)	22 (0.76)	6 (0.96)
Vascular disease	19 (1.16)	3 (1.60)	88 (3.04)	24 (3.82)
Stroke	12 (0.73)	4 (2.13)	50 (1.73)	9 (1.43)
Parkinson's disease	5 (0.31)	0 (0.00)	9 (0.31)	6 (0.96)
Diabetes				
No diabetes	1625 (99.21)	184 (97.87)	2854 (98.72)	620 (98.73)
Type 1	2 (0.12)	4 (2.13)	11 (0.38)	5 (0.80)
Type 2/unknown	11 (0.67)	0 (0.00)	26 (0.90)	3 (0.48)
Seizures	18 (1.10)	4 (2.13)	40 (1.38)	9 (1.43)
Epilepsy	10 (0.61)	2 (1.06)	28 (0.97)	7 (1.11)
MS characteristics				
Year of MS diagnosis (%)				
1945–1980			132 (4.57)	30 (4.78)
1981–1990			291 (10.07)	71 (11.31)
1991–2000			1122 (38.81)	265 (42.20)
2001–2005	138 (8.42)	17 (9.04)	1346 (46.56)	262 (41.72)
2006–2007	531 (32.42)	79 (42.02)		
2008–2009	438 (26.74)	61 (32.45)		
2010–2011	376 (22.95)	23 (12.23)		
2012–2014	155 (9.46)	8 (4.26)		
MS disease course (%)				
Relapsing remitting	1365 (83.33)	101 (53.72)	1878 (64.96)	244 (38.85)
Primary progressive	71 (4.33)	39 (20.74)	179 (6.19)	92 (14.65)
Secondary progressive	85 (5.19)	36 (19.15)	743 (25.70)	278 (44.27)
Unknown	117 (7.14)	12 (6.38)	91 (3.15)	14 (2.23)
Mean age at MS diagnosis, years (SD, min-max)	39.24 (0.26, 18.02–64.82)	44.57 (0.73, 19.93–64.71)	39.20 (0.20, 18.04–64.88)	40.56 (0.43, 18.09–64.86)
Onset N (% missing)	1464 (10.62)	172 (8.51)	2608 (9.79)	576 (8.28)
Mean age at MS onset, years (SD, min-max)	35.20 (0.27, 8.75–63.59)	38.57 (0.76, 15.54–62.29)	32.76 (0.19, 6.13–62.92)	33.62 (0.42, 11.75–62.46)
No of relapses N (% missing)	1007 (26.82)	323 (28.22)	2378 (17.74)	490 (21.97)
0 relapses (%)	104 (10.33)	29 (8.98)	77 (3.24)	15 (3.06)
1 relapse (%)	624 (61.97)	205 (63.47)	1400 (58.87)	299 (61.02)
2 relapses (%)	190 (18.87)	54 (16.72)	355 (14.93)	60 (12.24)
3 relapses (%)	55 (5.46)	22 (6.81)	213 (8.96)	44 (8.98)
4+ relapses (%)	34 (3.38)	13 (4.02)	333 (14.00)	72 (14.69)
First DMT N (% missing)	1198 (26.86)	132 (29.79)	2450 (15.25)	482 (23.25)
No DMT (%)	69 (4.80)	18 (13.04)	422 (17.22)	93 (19.29)
Moderately effective (%)	1195 (83.16)	104 (75.36)	1956 (79.84)	379 (78.63)
Highly effective (%)	173 (12.04)	16 (11.59)	72 (2.94)	10 (2.07)
Median years to first DMT, (IQR)	0.13 (0.05–0.36)	0.11 (0.04–0.26)	1.03 (0.18–4.90)	0.96 (0.13–5.03)
EDSS N (% missing)	739 (54.88)	75 (60.11)	1792 (38.01)	395 (37.10)
0 (%)	155 (20.97)	0 (0.00)	253 (14.12)	8 (2.03)
1–1.5 (%)	237 (32.07)	9 (12.00)	389 (21.71)	30 (7.59)
2–2.5 (%)	202 (27.33)	23 (30.67)	358 (19.98)	73 (18.48)

Continued

Table 1 Continued

Baseline characteristics	Incident MS N=1826		Prevalent MS N=3519	
	No Baclofen	Baclofen	No Baclofen	Baclofen
3–3.5 (%)	96 (12.99)	25 (33.33)	292 (16.29)	58 (14.68)
4–4.5 (%)	33 (4.47)	6 (8.00)	148 (8.26)	39 (9.87)
5–5.5 (%)	5 (0.68)	7 (9.33)	95 (5.30)	30 (7.59)
6–6.5 (%)	10 (1.35)	4 (5.33)	182 (10.16)	118 (29.87)
7–9.5 (%)	1 (0.14)	1 (1.33)	75 (4.19)	39 (9.87)

For many of the MS characteristics, there were missing values in each of the variables of interest. The percentage missing is listed in the table for each given variable.  
 \*No individuals had a diagnosis of cerebral palsy or amyotrophic lateral sclerosis.  
 DMT, disease-modifying therapy; EDSS, Expanded Disability Severity Scale; max, maximum; min, minimum; MS, multiple sclerosis; N, total number of individuals; TBI, traumatic brain injury.

discontinued overall. Among pwIMS and pwPMS and using a gap period of 150 days between prescriptions, 65% discontinued within the first year. Differences between pwIMS and pwPMS were only evident when stratifying by disease course as pwIMS with progressive courses continued longer than RRMS, though among pwPMS the differences in discontinuation between disease courses were less clear. Stratification by EDSS in either the pwIMS or pwPMS cohorts showed individuals of higher EDSS persisting longer on baclofen.

Discontinuation of other spasticity treatments

Discontinuation of gabapentin, diazepam or baclofen among pwIMS (whichever was prescribed first) also occurred rapidly after initiation (online supplemental figures 2–4). Gabapentin

was discontinued by 75% of individuals after 1 year, and diazepam nearly completely discontinued after 6 months, and identically as the main analyses for baclofen. Too few individuals received clonazepam or cannabinoids to determine their discontinuation.

DISCUSSION

To the best of our knowledge, this is the first study consisting of a real-world MS population followed for a period of 10 years capturing routine clinical practice in treating spasticity among both incident and prevalent patients with MS. Baclofen remains the first-line option for managing spasticity in MS, and patterns of initiation and discontinuation described in this study are relevant to inform future clinical practice. Newly diagnosed pwMS

Table 2 Individuals with incident MS and general variable associations with initiation of baclofen treatment

	Events	PT	M1		M2		M3		M4		M5		M6	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Sex														
Male	72	2821	1.00		1.00		1.00		1.00		1.00		1.00	
Female	116	7618	0.63	0.47 to 0.85	0.64	0.47 to 0.86	0.75	0.55 to 1.02	0.73	0.53 to 1.00	0.75	0.55 to 1.02	0.76	0.56 to 1.03
Disease course														
RRMS	83	8286					1.00		1.00		1.00		1.00	
PPMS	39	509					7.17	4.69 to 10.97	6.95	4.44 to 10.87	6.92	4.52 to 10.60	7.00	4.58 to 10.70
SPMS	54	887					5.57	3.82 to 8.13	5.90	3.95 to 8.82	5.57	3.82 to 8.13	5.64	3.86 to 8.24
Unknown	12	756					1.64	0.89 to 3.03	1.28	0.55 to 2.95	1.63	0.88 to 3.01	1.63	0.88 to 3.00
Age at MS onset	172	9446							1.00	0.98 to 1.03				
Time with MS														
<0.5	20	799									1.00			
≥0.5 to <1	19	859									0.99	0.52 to 1.89		
≥1 to <2	28	1762									0.67	0.37 to 1.22		
≥2 to <3	26	1652									0.68	0.37 to 1.24		
≥3 to <6	68	3759									0.73	0.43 to 1.23		
≥6	27	1608									0.61	0.33 to 1.12		
Year of MS diagnosis														
2005	17	1232											1.00	
2006–2007	79	4471											1.17	0.69 to 2.00
2008–2009	61	2807											1.56	0.90 to 2.71
2010–2011	23	1558											1.24	0.66 to 2.36
2012–2014	8	371											1.81	0.76 to 4.33

Individuals with incident MS (N=1826) ever treated with baclofen (n=188) for their spasticity as the outcome. All models adjusted for age, county of residence at MS diagnosis and highest attained educational level. Stratified Cox models used to account for non-proportionality in region of residence at MS diagnosis over time. Disease course and years with MS are time-varying covariates. Due to missing onset information (n=190), the model with age at onset includes N=1636 individuals.

The reference category is identified by an HR of 1.00 with no CI.

M, model; MS, multiple sclerosis; PPMS, primary progressive MS; PT, person time; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

**Table 3** Individuals with prevalent MS and general variable associations with initiation of baclofen treatment

	Events	PT	M1		M2		M3		M4		M5		M6		M7	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Sex																
Male	207	6616	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Female	421	20154	0.67	0.57 to 0.79	0.68	0.57 to 0.80	0.76	0.64 to 0.90	0.76	0.64 to 0.90	0.74	0.62 to 0.88	0.76	0.64 to 0.90	0.76	0.64 to 0.89
Disease course																
RRMS	179	15730					1.00		1.00		1.00		1.00		1.00	
PPMS	92	1804					5.59	4.25 to 7.34	5.49	4.18 to 7.22	5.45	4.10 to 7.25	5.54	4.22 to 7.28	5.55	4.22 to 7.30
SPMS	343	8426					4.32	3.54 to 5.27	4.41	3.61 to 5.39	4.36	3.52 to 5.39	4.40	3.60 to 5.38	4.34	3.55 to 5.31
Unknown	14	811					1.71	0.99 to 2.96	1.67	0.97 to 2.89	1.69	0.79 to 3.63	1.67	0.97 to 2.89	1.70	0.98 to 2.94
Age at MS diagnosis	628	26770							1.01	1.00 to 1.02						
MS-onset age	576	24212									1.01	1.00 to 1.02				
Time with MS																
1 to <3	40	1822											1.00			
≥3 to <5	73	3230											0.89	0.48 to 1.63		
≥5 to <7	87	3979											0.87	0.49 to 1.54		
≥7 to <9	100	4130											0.82	0.46 to 1.44		
≥9 to <11	73	3430											0.88	0.50 to 1.55		
≥11 to <13	53	2352											0.74	0.42 to 1.32		
≥13 to <15	187	7201											0.74	0.41 to 1.34		
≥15+	30	1208											0.76	0.44 to 1.33		
Year of MS diagnosis																
1945–1980	71	2687													0.93	0.62 to 1.40
1981–1990	265	10427													0.90	0.68 to 1.19
1991–2000	262	12449													1.02	0.85 to 1.21
2001–2005	207	6616													1.00	

Individuals with prevalent MS (N=3519), including individuals ever treated for their spasticity using baclofen (n=628). All models adjusted for age, county of residence at MS diagnosis and highest attained educational level. Disease course and years with MS are time-varying covariates. Due to missing onset information (n=335), the model with age at onset includes N=3184 individuals. Reference categories are indicated by an HR of 1.00 with no CI.

M, model; MS, multiple sclerosis; PPMS, primary progressive MS; PT, person time; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

and individuals with MS for many years can receive treatment for spasticity. MS is the likely cause for requiring baclofen as no other disease known to cause spasticity is associated with baclofen. EDSS measured any time after MS diagnosis is a strong predictor of baclofen prescription, especially among younger patients and this was irrespective of changes to EDSS. Younger compared with older patients with MS of similar disability showed different patterns of spasticity treatment as younger patients were more likely to start baclofen. All associations were observed even after finely controlling for time with MS, demonstrating that although MS severity tends to increase over time, it is disability and likely motor symptoms that contribute to the need for baclofen. Progressive disease course was also highly associated with baclofen treatment, first only among males, but these sex differences were eliminated after adjustment for MS characteristics. Baclofen initiation among pwMS is highest within 6 months from diagnosis, and among pwPPMS, within the first 3 years after diagnosis although this may reflect patients with prevalent disease reinitiating baclofen use after an initial rapid discontinuation as seen in this study. The vast majority of individuals treated with baclofen rapidly discontinued use, with more than 50% discontinuing within 6 months. This high rate of discontinuation even among more disabled patients and those with progressive disease demonstrates the lack of efficacy or tolerability of baclofen and other spasticity treatments, in turn leading to a low success rate of treating and managing spasticity with current pharmacological agents.

There were indications that even at low EDSS levels spasticity may affect pwMS, particularly at younger ages. Some 30% of baclofen prescriptions were given to both pwMS and pwPPMS

with EDSS scores less than three. However, as we are measuring treatment rather than spasticity directly, prescriptions may be to treat pain mistaken for spasticity, spasticity at a very low severity or to treat suspected spasticity resulting in discontinuation after no improvement or due to side effects. EDSS measurement error may also be a factor, as updates to EDSS can be delayed, or are not updated. Given the wide range of symptoms of spasticity, increases in muscular tone may not be the first indications of spasticity and as MS progresses, spasticity may manifest more apparently at a clinically significantly detectable level. Nonetheless, this highlights the importance of early identification and diagnosis of spasticity among pwMS given we observed an association with increasing age at MS onset and baclofen initiation, in order to advise on non-pharmacological treatments at very mild levels of spasticity or pain to reduce debilitating symptoms prior to needing baclofen given its side effects and need for it at a more severe level of disability. Cannabinoids represents a more recent pharmacological treatment option for MS-associated spasticity, where an oral preparation of delta-9-tetrahydrocannabinol has been approved by the European Medicines Agency. However, its use in Sweden is very limited and it is not included in the national drug reimbursement programme. In our study, only four patients have been prescribed this type of cannabinoid. Nevertheless, further studies in other cohorts should address whether the tolerability profile of cannabinoids is superior to that of current first-line and second-line pharmacological treatments.

Previous studies have largely suggested that spasticity is more common among people who have had MS for a longer period of time, among males and especially among individuals with

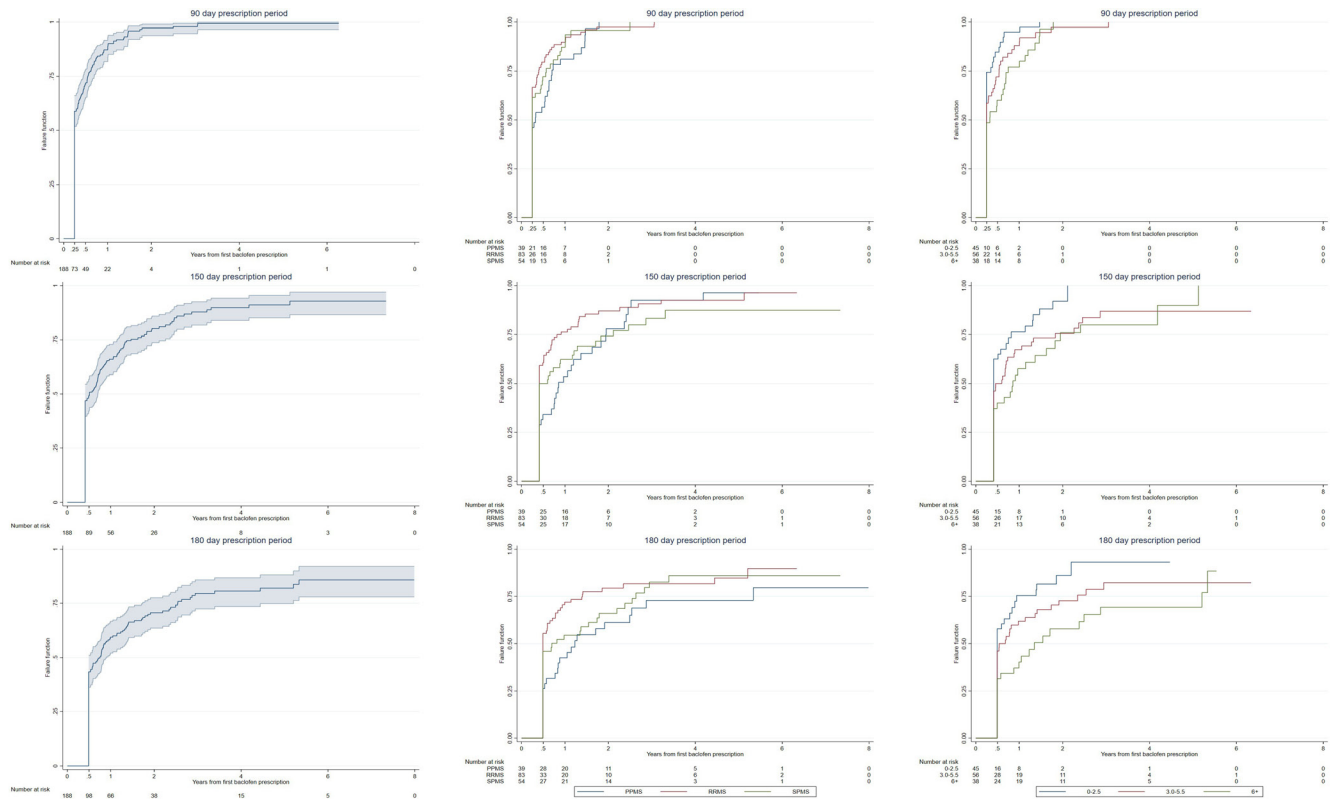
**Table 4** Incident MS—Association of Expanded Disability Severity Scale (EDSS) scores as a baseline and time-varying variable and other MS characteristics to baclofen treatment

Panel A: baseline EDSS		M1		M2		M3		M4		M5		M6		M7								
E	PT	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI							
EDSS																						
EDSS 0–2.5	32	3711	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00							
EDSS 3–5.5	38	895	3.85	2.35 to 6.31	3.78	2.29 to 6.26	3.50	2.09 to 5.84	2.89	1.70 to 4.93	3.05	1.61 to 5.76	3.13	1.69 to 5.78	3.07	1.62 to 5.80						
EDSS 6+	5	75	4.66	1.73 to 12.59	4.33	1.59 to 11.80	3.83	1.38 to 10.61	2.94	1.06 to 8.16	2.74	0.51 to 14.65	2.99	0.62 to 14.47	2.49	0.46 to 13.58						
Sex																						
Male	27	1239	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00						
Female	48	3442	0.83	0.51 to 1.35	0.84	0.51 to 1.38	0.83	0.50 to 1.37	0.86	0.52 to 1.43	1.15	0.61 to 2.16	1.09	0.59 to 2.04	1.15	0.61 to 2.16						
Age at MS onset	72	4447	1.02	0.99 to 1.05	1.02	0.99 to 1.05	1.02	0.99 to 1.05	1.03	0.99 to 1.07	1.02	0.98 to 1.06	1.01	0.97 to 1.04	1.02	0.98 to 1.07						
Course at entry																						
RRMS	38	3912	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00						
PPMS	14	180	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00						
SPMS	20	345	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00						
Unknown	3	243	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00						
DMT use																						
No DMT	9	546	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00						
Moderately effective	36	3162	1.48	0.60 to 3.67	1.48	0.60 to 3.67	1.48	0.60 to 3.67	1.48	0.60 to 3.67	1.48	0.60 to 3.67	0.89	0.39 to 2.00	1.39	0.54 to 3.57						
Highly effective	9	434	1.19	0.40 to 3.56	1.19	0.40 to 3.56	1.19	0.40 to 3.56	1.19	0.40 to 3.56	1.19	0.40 to 3.56	0.94	0.32 to 2.75	1.13	0.36 to 3.53						
Panel B: time-varying EDSS																						
E	PT	HR	95% CI	M2	HR	95% CI	M3	HR	95% CI	M4	HR	95% CI	M5	HR	95% CI	M6	HR	95% CI	M7	HR	95% CI	
EDSS																						
0–2.5 age 18–44	22	4479	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
0–2.5 age 45–73	23	2196	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
3–5.5 age 18–44	21	701	5.33	2.88 to 9.87	5.91	3.20 to 10.92	5.90	3.22 to 10.83	5.59	3.06 to 10.20	5.49	2.86 to 10.53	5.60	2.92 to 10.73	5.62	2.92 to 10.73	5.60	2.92 to 10.73	5.62	2.91 to 10.85	5.62	2.91 to 10.85
3–5.5 age 45–73	35	1131	2.76	1.62 to 4.71	2.47	1.44 to 4.23	2.38	1.38 to 4.10	1.99	1.14 to 3.48	2.07	1.11 to 3.84	2.31	1.25 to 4.26	2.05	1.10 to 3.82	2.31	1.25 to 4.26	2.05	1.10 to 3.82	2.05	1.10 to 3.82
6+ age 18–44	13	118	18.83	9.61 to 36.88	20.66	10.18 to 41.95	23.66	11.88 to 47.15	17.84	9.32 to 34.15	15.61	7.22 to 33.75	18.28	8.21 to 40.67	15.41	7.07 to 33.58	18.28	8.21 to 40.67	15.41	7.07 to 33.58	15.41	7.07 to 33.58
6+ age 45–73	25	244	9.31	5.15 to 16.82	8.13	4.45 to 14.85	7.76	4.24 to 14.22	5.13	2.76 to 9.52	4.27	1.99 to 9.18	6.29	3.03 to 13.05	4.26	1.97 to 9.17	6.29	3.03 to 13.05	4.26	1.97 to 9.17	4.26	1.97 to 9.17
Sex																						
Male	50	2334	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
Female	89	6535	0.82	0.58 to 1.17	0.79	0.56 to 1.13	0.81	0.57 to 1.15	0.86	0.61 to 1.23	0.90	0.60 to 1.33	0.96	0.64 to 1.44	0.94	0.62 to 1.42	0.96	0.64 to 1.44	0.94	0.62 to 1.42	0.94	0.62 to 1.42
Age at MS onset	132	8264	1.00	0.98 to 1.02	1.00	0.98 to 1.02	1.00	0.98 to 1.02	1.01	0.99 to 1.03	1.01	0.98 to 1.03	1.00	0.98 to 1.02	1.01	0.98 to 1.04	1.00	0.98 to 1.02	1.01	0.98 to 1.04	1.01	0.98 to 1.04
Disease course																						
RRMS	80	7450	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
PPMS	27	411	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
SPMS	29	604	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
Unknown	3	403	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
DMT use																						
No DMT	17	1095	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
Moderately effective	79	6263	1.31	0.75 to 2.28	0.92	0.53 to 1.59	1.31	0.75 to 2.28	0.92	0.53 to 1.59	1.31	0.75 to 2.28	0.92	0.53 to 1.59	1.31	0.75 to 2.28	0.92	0.53 to 1.59	1.31	0.75 to 2.28	0.92	0.53 to 1.59
Highly effective	13	672	1.32	0.60 to 2.91	1.32	0.60 to 2.91	1.32	0.60 to 2.91	1.32	0.60 to 2.91	1.32	0.60 to 2.91	1.32	0.60 to 2.91	1.32	0.60 to 2.91	1.32	0.60 to 2.91	1.32	0.60 to 2.91	1.32	0.60 to 2.91

Reference categories indicated by HRs of 1.00 with no 95% CI. Panel A: Association of baseline EDSS to baclofen treatment. Model 1 adjusted for age, county of residence at MS diagnosis and highest attained education. Model 3 additionally adjusted for time with MS as an additional timescale. Disease-modifying treatment is a time-varying variable. Due to missing values, the number of individuals vary. Model 1 (N=814), models 2–4 (N=767), models 5–7 (N=672). Panel B: Association of time-varying EDSS to baclofen. Due to violation of the proportional hazard assumption, an interaction between age (timescale) and EDSS was used. Reference categories are the lowest EDSS category at each respective age group as compared with the next EDSS level in that specific age group. Model 1 adjusted for age, county of residence at MS diagnosis and highest attained education. Model 3 additionally adjusted for time with MS as an additional timescale. Due to missing values, the number of individuals vary. Model 1 (N=1514), models 2–4 (N=1402) and models 5–7 (N=1281). Disease-modifying treatments is a time-varying variable. Robust SE used to calculate confidence intervals due to repeated measurements of EDSS. RRMS, relapsing remitting MS; PT, per centime; PPMs, progressive MS; SPMS, secondary progressive MS; DMT, disease-modifying therapy; E, number of events; HR, Hazard ratio; M, model; PPMs, primary progressive MS; PT, per centime; RRMS, relapsing remitting MS; SPMS, secondary progressive MS.







**Figure 3** Time to discontinuation of baclofen among people with incident multiple sclerosis stratified by disease course and Expanded Disability Severity Scale (EDSS). Left column, overall discontinuation. Middle column, discontinuation stratified by disease course when starting baclofen. Right column, discontinuation stratified by EDSS score when starting baclofen. PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

a progressive course.<sup>4</sup> This was also true here; however, sex differences disappeared after adjusting for MS characteristics. We also show that a large proportion of individuals receiving baclofen have RRMS and that pwMS require spasticity treatment early after MS diagnoses and at younger ages. Progressive disease courses showed higher magnitude associations with baclofen treatment, which is unsurprising given the increasing motor symptoms and disability accompanying progressive MS. However, the occurrence of spasticity indicated by treatment in our study is much lower than self-reported prevalence in another study.<sup>22</sup> This may reflect us capturing more severe spasticity requiring baclofen as well as we do not capture non-prescription treated spasticity. At lower levels of spasticity severity, treatments can be both over-the-counter or non-pharmacological until spasticity can no longer be managed,<sup>23 24</sup> something we are unable to capture in this study. It is also possible that other studies where spasticity is self-reported, PwMS may attribute a wider range of symptoms to spasticity, while treating neurologists rely more on objective findings such as increased muscle tone. We believe that no other study has directly examined the time to rapid discontinuation of baclofen as we assessed in our study, but other studies discuss discontinuation. Discontinuation is likely due to the low tolerability of the treatments given their wide-range of side effects such as dizziness or low blood pressure.<sup>25 26</sup>

Broadening the definition of spasticity treatments attenuated the magnitude of associations observed with baclofen. However, baclofen may not be the first choice for spasticity treatment especially among individuals with RRMS. Treatments such as gabapentin and diazepam can be prescribed for spasticity as shown in other studies<sup>4 6</sup> although we cannot be

sure of the reason for their prescription in our study. Although they are primarily indicated for treatment of neuropathic pain, gabapentin has been shown to effectively relieve spasticity and spasticity-related pain.<sup>8</sup> Not all patients are able to be treated with baclofen, as drug–drug interactions can occur between baclofen, tricyclic antidepressants and antihypertensives.

Studies among general populations have shown that stroke, head trauma and other diseases increased the risk of spasticity,<sup>5 27 28</sup> although this could not be verified in this MS population. This instead points to MS-specific spasticity due to pathological changes caused by MS. pwMS overall had larger magnitude associations if they had comorbid diseases compared with pwPMS, but pwPMS were much older: age could be the more important factor that reduces the associations as older adults experience a larger comorbid disease burden in general,<sup>29</sup> reducing differences among treatment groups. The results could also be explained by an increased number of contacts with healthcare increasing the probability of receiving a treatment for spasticity, however it is likely an actual increase in spasticity for those with additional comorbid diseases as results are similar among both pwMS and pwPMS. Additionally, the age-related differences we observed between younger and older similarly disabled patients could be due to an increased sensitivity to side effects among older patients, or that older patients may have a greater perceived or real risk of falling when treating for spasticity as spasticity-associated muscle rigidity can provide a degree of postural stability. Collectively, this may lead to reduced tolerability compared with younger individuals with similar disability level.

## Advantages and disadvantages

This large, register-based study is the first to our knowledge to include both incident and prevalent MS cohorts. Baclofen treatment was not subject to recall bias or lost to follow-up as all individuals were followed throughout the study period. We examined a wide variety of possible MS characteristics, comorbid diseases and individual factors, which were not subject to types of bias found in self-reported studies. Although we were not able to confirm if individuals had spasticity when receiving baclofen, baclofen is used almost exclusively to treat spasticity in patients with MS in Sweden. The only exception being that baclofen is also considered a second-line option in guidelines from the Swedish Medical Products Agency for painful Lhermitte and trigeminal neuralgia (together with gabapentin, lamotrigine and phenytoin),<sup>10</sup> two conditions known to affect only a minority of patients with MS. We also broadened the definition of spasticity treatment to other pharmacological treatments that have broader indications including pain, and performed multiple sensitivity analyses to exclude comorbid diseases and counter-indicated prescriptions that confirmed the main results and ensured a good approximation of spasticity by using treatment as a proxy for spasticity. The severity of spasticity could not be captured, however we likely captured spasticity that is more severe in nature especially among pwPMS, but very severe spasticity was likely not captured here as intrathecal baclofen pumps, Botox injections and second-line treatments were not identified. These are not usually a first treatment choice for spasticity over oral baclofen or the other preparations used to identify spasticity in this study. Nevertheless, in both cohorts, spasticity is likely underestimated rather than overestimated as over-the-counter medications for pain and non-pharmacological treatments are not captured. Among the prevalent population in particular, we may be underestimating spasticity as individuals prior to 2005 (when the PDR began) could have had an initial spasticity treatment that we cannot observe, however, they were still eligible to receive another prescription during the study period.

Associations of specific DMTs with baclofen could not be explored in this study, as most individuals received interferon treatments or glatiramer acetate. The study period did not cover the years in which more highly effective DMTs became more commonly prescribed rather than reserved for individuals with more severe MS or as escalation therapies. The individuals most likely to receive highly effective DMTs had more severe MS and thus were more likely to have spasticity, which largely explains the increased HRs of DMT with baclofen initiation.

## CONCLUSION

pwMS can require treatment for spasticity even early post-MS diagnosis, at lower levels of MS disability and at young ages. High rates of discontinuation of treatment highlights an unmet need of tolerable and effective spasticity treatment alternatives. Taken together, this further highlights the importance of informed treatment options and better understanding of spasticity in general among patients with MS.

**Correction notice** Since this paper was first published, the author surname Strid has been updated to Stridh.

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**Ethics approval** Approval was given by the Regional Ethics Review Board at Karolinska Institute (2013/574-31/4). Participants gave informed consent to participate in the study before taking part.

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## ORCID iDs

Kelsi A Smith <http://orcid.org/0000-0002-9811-908X>

Jan Hillert <http://orcid.org/0000-0002-7386-6732>

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**Supplementary Table 0: ICD-10 codes used to identify diseases from the National Patient Register and Anatomical Therapeutic Chemical (ATC) codes used to identify prescriptions from the Prescribed Drug Register to classify individuals with a specific disease.**

Disease category	National Patient Register ICD-10 diagnoses. Codes in <b>bold</b> were extracted from the register.	Prescribed Drug Register ATC prescription codes. Codes in <b>bold</b> were extracted from the register.	Drug name	How individuals were identified with the disease	Reason for disease inclusion
<b>Amyotrophic lateral sclerosis (ALS)</b>	<b>G12.2</b>			The first diagnosis of ALS within the National Patient Register was used as the date of diagnosis of ALS. Given the speed as to which ALS progresses, individuals were also identified from the Cause of Death register using the same ICD-10 code.	Individuals with either or ALS and cerebral palsy have been shown to have spasticity.
<b>Cardiovascular diseases and disorders</b> <sup>1</sup>	<b>Vascular hypertensive disorders: I10-I13, I15</b> <b>Coronary artery disorders: I20-I25</b>			First recorded diagnosis of either disease was used as the date of vascular hypertension, or coronary artery disease.	Vascular hypertensive disorders and coronary artery disorders are risk factors for stroke. Individuals who have experience a stroke are more likely to have spasticity.
<b>Cerebral palsy</b>	<b>G80</b>			The earliest date of diagnosis in the National Patient Register was used to identify individuals with cerebral palsy.	Individuals with cerebral palsy are known to have spasticity.
<b>Depression</b> <sup>2</sup>  NOTE: the drug names are the ones currently recommended for use in Sweden under treatment guidelines. The ATC prescription categories contain more ATC codes, with drugs used previously. Both	<b>F31 – Bipolar affective disorder</b>  <b>F32: Depressive episode</b> F32.0 – Mild depressive symptom F32.1 – Moderate depression F32.2- Severe without psychotic episode F32.3- Severe with psychotic episode F32.8 – Other depressive episodes F32.9 – Depressive episode, unspecified  <b>F33: Recurrent depressive episode</b> <b>F33.0</b> — Mild	<b>‘N06A’ +(A-G,X)</b> <b>TCA: ‘N06AC’</b>  N06AA09 N06AA04 N06AA21, ‘N06AC01 N06AA10  <b>SSRI: ‘N06AB’</b>  N06AB04 N06AB10 N06AB03 N06AB08 N06AB05 N06AB06	<b>Antidepressants</b> <b>TCA: (Tricyclic antidepressants)/Non-specific monoamine oxidase inhibitors</b> Amitriptyline Clomipramine Maprotiline Nortriptyline  <b>SSRI: (Selective serotonin reuptake inhibitors)</b> Citalopram Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	First ever date of prescription or of diagnosis used to identify depression. Earliest date of prescription or diagnosis used as the date of the start of depression.	Some of the spasticity treatments are also indicated for anxiety and pain, among other diseases/conditions. Therefore, it is important to identify individuals with depression to determine the overlap between depression and spasticity treatments/diagnoses. Depression can also increase pain, a symptom that is also associated with spasticity.  Some spasticity treatments, such as baclofen, are counter indicated for use with tricyclic antidepressants, which may lead to use of other spasticity

<sup>1</sup> Treatment of cardiovascular diseases in Sweden: <https://www.lakemedelsverket.se/globalassets/dokument/behandling-och-forskrivning/behandlingsrekommendationer/behandlingsrekommendation/behandlingsrekommendation-att-forebygga-aterosklerotisk-hjart-karlsjukdom-med-lakemedel.pdf>

<sup>2</sup> Treatment of depression in Sweden: <https://www.lakemedelsverket.se/globalassets/dokument/behandling-och-forskrivning/behandlingsrekommendationer/behandlingsrekommendation/behandlingsrekommendation-lakemedel-depression-angestsyndrom-tvangssyndrom.pdf>



are included for completeness.	<b>F33.1</b> – moderate <b>F33.2</b> – severe with psychotic <b>F33.3</b> – severe without psychotic <b>F33.8</b> – other <b>F33.9</b> – unspecified  <b>F34</b> – Persistent mood disorders <b>F38</b> – Other mood disorders <b>F39</b> – Unspecified mood disorder	<b>MAOI: ‘N06AF’, ‘N06AG’</b>  N06AG02  <b>Other: ‘N06AX’</b>  N06AX03 N06AX11  <b>Other: ‘N06AX’</b>  N06AX21 N06AX16  N06AX12 N06AX18  N06AX22  N06AX26	<b>MAOI: (Monoamine oxidase inhibitor)</b> Moclobemide  <b>NaSSA: (Noradrenergic and specific serotonergic antidepressants)</b> Mianserin Mirtazapine  <b>SNRI: (Serotonin norepinephrine reuptake inhibitors)<sup>3</sup></b> Duloxetine Venlafaxine  <b>Other:</b> Bupropion Reboxetine (Noradrenergic reuptake inhibitors) Agomelatine (limited use in Sweden) Vortioxetine (limited use in Sweden)		pharmacological treatments instead of baclofen.
<b>Diabetes</b>	<b>E10</b> – Type I diabetes <b>E11</b> – Type II diabetes <b>E13</b> – Other specified diabetes <b>E14</b> – Non-specific diabetes			Individuals with ICD-10 codes of E13 and E14 combined together into “unknown” diabetes category. In the event of multiple diagnoses, the earliest date of diabetes diagnosis was used.	Diabetes is a risk factor for both cardiovascular diseases and stroke, both possibly leading to an increased risk in spasticity.
<b>Epilepsy Seizures</b> <sup>4</sup>	G40 G41	Anti-epileptics were not available.		Individuals with at least two diagnoses of seizure/epilepsy were used to identify individuals with epilepsy, as there is considerable overlap between both ICD-10 codes.	Seizures among people with MS have been previously shown to be associated with spasticity.
<b>Stroke/TIA</b>	<b>Ischemic stroke:</b> I63, I64, I69*, G46** <b>Haemorrhagic stroke:</b> I60, I61, I62, I69*, G46** <b>TIA:</b> G45			Due to the limited number of individuals with stroke, all types of stroke were combined, and classified as ever vs never stroke. In the event of multiple diagnoses,	Individuals who have experienced a stroke are also likely to develop spasticity.

<sup>3</sup> For treatment of severe depression, SNRI (mainly venlafaxine) has been shown to be more effective than SSRIs.

<sup>4</sup> Treatment of seizures and epilepsy in Sweden: <https://www.lakemedelsverket.se/globalassets/dokument/behandling-och-forskrivning/behandlingsrekommendationer/behandlingsrekommendation/behandlingsrekommendation-epilepsi.pdf>

	*I69 includes sequelae of both ischemic and haemorrhagic stroke **Vascular syndromes of brain in cerebrovascular diseases could be both ischemic and haemorrhagic.			the first diagnosis was used as the date of stroke.	
<b>Traumatic brain injuries (TBI) causing bleeding due to external causes.</b>	S06.1, S06.3-S06.8* *All S chapter ICD codes are traumatic brain injury types of bleeding most similar to stroke, excluding concussion. Not included under stroke as these are due to external causes.			Concussion and TBI (first date of either) are combined into one variable as they were a rare occurrence among individuals in this study.	Concussions and TBI may be associated with spasticity.
<b>Concussion &amp; spinal cord injury</b>	S06.0 - Concussion S06.2 – Diffuse brain injury S06.9 – Intracranial injury, unspecified T90.5 – sequelae of intracranial injury  <b>Spinal cord injuries</b> T02.0 T02.1 T02.7 T03.0 T03.1 T04.0 T04.1 T06.0 T06.1 T08 T09.3			Concussion and TBI (first date of either) are combined into one variable as they were a rare occurrence among individuals in this study.  <b>Note:</b> No one in the dataset had any of the spinal cord injury ICD codes. One person had a 4 <sup>th</sup> diagnosis of one of the codes, but likely a suspected spinal cord injury. Not include in further analyses.	Concussions and TBI may be associated with spasticity.
<b>Parkinson's disease</b>	G20 – Primary Parkinson's disease G21 – Secondary parkinsonism				Due to similar clinical presentation of tremors, rigidity and overlap with respects to possible mechanisms causing Parkinson's symptoms and Parkinson's like symptoms, it is possible that an individual receives an ICD code in hospital for Parkinson's disease.

**Supplementary Table 1: Baseline characteristics assessed at study entry of incident and prevalent individuals with MS, stratified by use of treatments for spasticity.**

<b>Baseline characteristics</b>	<b>Incident</b>		<b>Prevalent</b>	
	<b>No Spasticity</b>	<b>Spasticity</b>	<b>No Spasticity</b>	<b>Spasticity</b>
<b>N</b>	<b>1376</b>	<b>450</b>	<b>2347</b>	<b>1172</b>
<b>Type of treatment n(%)</b>				
Baclofen		138(30.67)		512(43.69)
Clonazepam		6(1.33)		39(3.33)
Diazepam		78(17.33)		231(19.71)
Gabapentin		226(50.22)		388(33.11)
Cannaboids		2(0.44)		2(0.17)
<b>Sex n( %)</b>				
Male	376(27.33)	133(29.56)	578(24.63)	324(27.65)
Female	1000(72.67)	317(70.44)	1769(75.37)	848(72.35)
<b>Highest attained education n( %)</b>				
Primary education	98(7.12)	55(12.22)	269(11.46)	193(16.47)
Secondary education	637(46.29)	227(50.44)	1087(46.31)	534(45.56)
Tertiary education	641(46.58)	168(37.33)	991(42.22)	445(37.97)
<b>Comorbid diseases n( %)</b>				
Amyotrophic lateral sclerosis	0(0.00)	0(0.00)	0(0.00)	1(0.09)
Depression	220(15.99)	114(25.33)	496(21.13)	384(32.76)
Concussion or TBI	2(0.15)	1(0.22)	4(0.17)	4(0.34)
Coronary artery disease	1(0.07)	1(0.22)	18(0.77)	10(0.85)
Vascular disease	13(0.94)	9(2.00)	68(2.90)	44(3.75)
Stroke	12(0.87)	4(0.89)	38(1.62)	21(1.79)
Parkinson's disease	3(0.22)	2(0.44)	4(0.17)	11(0.94)
Diabetes				
No diabetes	1364(99.13)	445(98.89)	2317(98.72)	1157(98.72)
Type 1	2(0.15)	4(0.89)	10(0.43)	6(0.51)
Type 2	9(0.65)	1(0.22)	18(0.77)	8(0.68)
Type unknown	1(0.07)	0(0.00)	2(0.09)	1(0.09)
Seizure	16(1.16)	6(1.33)	25(1.07)	24(2.05)
Epilepsy	9(0.65)	3(0.67)	18(0.77)	17(1.45)
<b>MS Characteristics n( %)</b>				
<b>Year of MS diagnosis</b>				
1945-1980	0(0.00)	0(0.00)	115(4.90)	47(4.01)
1981-1990	0(0.00)	0(0.00)	241(10.27)	121(10.32)
1991-2000	0(0.00)	0(0.00)	886(37.75)	501(42.75)
2001-2005	117(8.50)	38(8.44)	1105(47.08)	503(42.92)
2006-2007	433(31.47)	177(39.33)	0(0.00)	0(0.00)
2008-2009	357(25.94)	142(31.56)	0(0.00)	0(0.00)
2010-2011	329(23.91)	70(15.56)	0(0.00)	0(0.00)
2012-2014	140(10.17)	23(5.11)	0(0.00)	0(0.00)
<b>MS Disease course n( %)</b>				
Relapsing remitting	1154(83.87)	312(69.33)	1545(65.83)	577(49.23)
Primary progressive	52(3.78)	58(12.89)	138(5.88)	133(11.35)
Secondary progressive	67(4.87)	54(12.00)	589(25.10)	432(36.86)
Unknown	103(7.49)	26(5.78)	75(3.20)	30(2.56)
Mean age at MS diagnosis, years(SD, min-max)	38.93(0.29, 18.06-64.82)	42.44(0.49, 18.02-64.71)	38.93(0.22, 18.04-64.88)	40.47(0.31, 18.09-64.86)
Onset n (% missing)	1229(10.68)	407(9.56)	2115(9.88)	1069(8.79)
Mean age at MS onset, years(SD, min-max)	34.74(0.29, 8.75-63.59)	38.01(0.51, 10.37-62.67)	32.54(0.21, 6.13-62.92)	33.65(0.31, 11.75-62.46)
<b>Number of relapses n( % missing)</b>	1007(26.82)	323(28.22)	1941(17.30)	927(20.90)
0 relapses	104(10.33)	29(8.98)	62(3.19)	30(3.24)
1 relapse	624(61.97)	205(63.47)	1125(57.96)	574(61.92)

<b>Baseline characteristics</b>	<b>Incident</b>		<b>Prevalent</b>	
	<b>No Spasticity</b>	<b>Spasticity</b>	<b>No Spasticity</b>	<b>Spasticity</b>
2 relapses	190(18.87)	54(16.72)	294(15.15)	121(13.05)
3 relapses	55(5.46)	22(6.81)	182(9.38)	75(8.09)
4+ relapses	34(3.38)	13(4.02)	278(14.32)	127(13.70)
First DMT n (% missing)*	1239(9.96)	336(25.33)	2011(14.32)	917(21.76)
No DMT use	58(4.68)	29(8.63)	357(17.73)	158(17.21)
Moderately effective DMT	1032(83.29)	267(79.46)	1595(79.20)	740(80.61)
Highly effective DMT	149(12.03)	40(11.90)	62(3.08)	20(2.18)
Median years to first DMT, (IQR)	0.14(0.05-0.37)	0.11(0.05-0.29)	1.00(0.19-4.93)	1.05(0.14-4.75)
EDSS n (% missing)	618(55.09)	196(56.44)	1473(37.24)	714(39.08)
0	140(22.65)	15(7.65)	219(14.87)	42(5.88)
1-1.5	203(32.85)	43(21.94)	329(22.34)	90(12.61)
2-2.5	158(25.57)	67(34.18)	302(20.50)	129(18.07)
3-3.5	81(13.11)	40(20.41)	239(16.23)	111(15.55)
4-4.5	26(4.21)	13(6.63)	119(8.08)	68(9.52)
5-5.5	5(0.81)	7(3.57)	77(5.23)	48(6.72)
6-6.5	4(0.65)	10(5.10)	131(8.89)	169(23.67)
7-9.5	1(0.16)	1(0.51)	57(3.87)	57(7.98)

**Abbreviations:** %=percentage; +=or more; DMT=disease modifying therapy; EDSS=expanded disability severity scale HR=hazard ratio; IQR=interquartile range; max=maximum; min=minimum; N=total number individuals ; n=total number in subgroup; Ref=reference group; SD=standard deviation; TBI=traumatic brain injury.

**Note:** For many of the MS characteristics, there were missing values in each of the variables of interest. The percentage missing are listed in the table for each given variable.

† Univariate Cox proportional hazard models were used to calculate hazard ratios using age as the underlying timescale. The hazard ratios can be interpreted as incidence rate ratios.

\* Given the status of disease modifying therapy (DMT) use can occur sometime after MS diagnosis, first DMT use was used as a time varying covariate (the value of the variable was allowed to change over time).

**Supplementary Table 2: Association of relapses to baclofen treatment among incident and prevalent MS individuals.**

<b>Incident MS</b>	<b>E</b>	<b>PT</b>	<b>M1 HR</b>	<b>95% CI</b>	<b>M2 HR</b>	<b>95% CI</b>	<b>M3 HR</b>	<b>95% CI</b>	<b>M4 HR</b>	<b>95% CI</b>	<b>M5 HR</b>	<b>95% CI</b>
<b>Relapses</b>												
No relapses	7	609	1.00		1.00		1.00		1.00		1.00	
1 relapse	56	4396	0.94	0.43,2.07	1.22	0.46,3.22	2.13	0.21,21.10	1.10	0.41,2.94	1.12	0.42,2.99
2 relapses	23	2054	0.98	0.41,2.31	1.35	0.49,3.74	2.52	0.25,24.87	1.09	0.38,3.10	1.10	0.39,3.15
<b>Age at MS onset</b>	82	6669			1.00	0.97,1.03	1.03	0.98,1.09	0.99	0.96,1.03	1.00	0.96,1.04
<b>EDSS at study entry</b>												
EDSS 0-2.5	22	2963					1.00					
EDSS 3-5.5	12	617					2.11	0.99,4.49				
EDSS 6+	1	35					1.98	0.21,18.59				
<b>DMT use</b>												
No DMT	3	659							1.00		1.00	
Moderately effective DMT	63	5275							2.70	0.83,8.79	2.77	0.82,9.33
Highly effective DMT	8	493							4.90	1.25,19.17	4.95	1.22,20.14

Individuals with incident MS diagnosed with RRMS with relapses (N=1146). Association of relapses at study entry to baclofen treatment. Model 1 adjusted for age, county of residence at MS diagnosis, and highest attained education. Model 2-5 additionally adjusted for number of years from MS onset to diagnosis and calendar year of MS diagnosis. Model 5 additionally adjusted for time with MS as an additional timescale. Disease modifying treatments are time-dependent variables. Note: varying number of individuals in each model due to missing values; Model 1 N=1146; Model 2 N=1077; Model 3 N=568; Model 4-5 N=908. Abbreviations: CI= confidence interval; DMT=disease modifying therapy; E=number of events; EDSS=Expanded Disability Severity Scale; HR=hazard ratio; M=model; PT=person-time. Reference category indicated by a hazard ratio of 1.00 with no confidence interval.

<b>Prevalent MS</b>	<b>E</b>	<b>PT</b>	<b>M1 HR</b>	<b>95% CI</b>	<b>M2 HR</b>	<b>95% CI</b>	<b>M3 HR</b>	<b>95% CI</b>	<b>M4 HR</b>	<b>95% CI</b>	<b>M5 HR</b>	<b>95% CI</b>
<b>Relapses</b>												
No relapse	11	516	1.00		1.00		1.00		1.00		1.00	
1 relapse	114	8053	0.75	0.40,1.41	0.77	0.41,1.44	1.25	0.30,5.23	0.88	0.44,1.75	0.90	0.45,1.79
2 relapses	33	2578	0.70	0.35,1.40	0.71	0.36,1.42	1.20	0.28,5.15	0.81	0.38,1.71	0.82	0.39,1.74
3 relapses	24	1552	0.83	0.40,1.72	0.85	0.41,1.76	1.03	0.23,4.63	0.88	0.40,1.93	0.89	0.40,1.96
4+ relapses	35	2445	0.79	0.40,1.58	0.80	0.40,1.58	1.44	0.34,6.13	0.90	0.43,1.91	0.92	0.43,1.94
<b>Age at MS diagnosis</b>	217	15144			0.99	0.95,1.04	0.99	0.94,1.05	0.99	0.95,1.04	1.05	0.94,1.18
<b>EDSS at study entry</b>												
EDSS 0-2.5	84	7629					1.00					
EDSS 3-5.5	43	2402					1.61	1.10,2.35				
EDSS 6+	11	155					6.54	3.44,12.45				
<b>DMT use</b>												
No DMT	16	1852							1.00		1.00	
Moderately effective DMT	183	11890							1.86	1.08,3.22	1.85	1.07,3.21
Highly effective DMT	5	240							2.81	1.00,7.88	2.77	0.99,7.79

Individuals with prevalent MS diagnosed with RRMS with relapses (N=1890). Association of relapses at study entry to baclofen treatment. Model 1 adjusted for age, county of residence at MS diagnosis, and highest attained education. Model 2-5 additionally adjusted for number of years from MS onset to diagnosis and calendar year of MS diagnosis. Model 5 additionally adjusted for time with MS as an additional timescale. Disease modifying treatments are time-dependent variables. Note: varying number of individuals in each model due to missing values. Model 1,2 N=1890, Model 3 N=1268 Models 4-5 N=1745. Abbreviations: CI= confidence interval; DMT=disease modifying therapy; E=number of events; EDSS=Expanded Disability Severity Scale; HR=hazard ratio; M=model; PT=person-time. Reference category indicated by a hazard ratio of 1.00 with no confidence interval.





**Supplementary Table 3: Individuals with incident MS and general variable associations with spasticity treatment.**

	Event s	PT	M1		M2		M3		M4*		M5		M6	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<b>Sex</b>														
Male	132	2518	1.00		1.00		1.00		1.00		1.00		1.00	
Female	316	6701	0.93	0.76,1.14	0.97	0.79,1.19	1.07	0.87,1.32	1.03	0.83,1.28	1.08	0.87,1.32	1.08	0.88,1.33
<b>Education</b>														
Compulsory	55	697			1.00		1.00		1.00		1.00		1.00	
Post-compulsory	226	4421			0.66	0.49,0.89	0.70	0.52,0.94	0.65	0.48,0.89	0.73	0.54,0.99	0.72	0.53,0.98
Tertiary	167	4101			0.52	0.38,0.71	0.56	0.41,0.76	0.57	0.41,0.79	0.59	0.43,0.81	0.57	0.42,0.79
<b>Disease course †</b>														
RRMS	298	7358					1.00		1.00		1.00		1.00	
PPMS	57	417					3.18	2.34,4.34	2.85	2.06,3.95	2.75	2.02,3.75	3.09	2.27,4.22
SPMS	67	750					2.22	1.67,2.95	2.70	2.00,3.63	2.21	1.66,2.94	2.26	1.70,3.01
Unknown	26	694					0.89	0.59,1.33	0.80	0.48,1.36	0.89	0.60,1.33	0.88	0.59,1.32
<b>Age at MS onset</b>	405	8325							1.04	1.02,1.06				
<b>Years with MS †</b>														
<0.5	108	768									1.00			
≥0.5 to <1	46	806									0.40	0.28,0.57		
≥1 to <2	82	1613									0.35	0.26,0.47		
≥2 to <3	62	1471									0.30	0.22,0.40		
≥3 to <6	112	3206									0.24	0.18,0.31		
≥6	38	1356									0.18	0.13,0.27		
<b>MS diagnosis year</b>														
2005	38	1130											1.00	
2006-2007	177	3921											1.30	0.92,1.85
2008-2009	141	2402											1.76	1.23,2.53
2010-2011	70	1420											1.51	1.01,2.25
2012-2014	22	346											1.99	1.17,3.38

**Abbreviations:** CI=confidence interval; HR=hazard ratio; M=model; RRMS=relapsing remitting MS; PT=person-time; PPMS=primary progressive MS; SPMS; secondary progressive MS.

Individuals with incident MS (N=1822) additionally excluding individuals with PPMS/SPMS diagnosed ≤ 25 year of age (n=4). All models are adjusted for age and county of residence at MS diagnosis. Variable categories with hazard ratios of 1.00 without confidence intervals are reference categories.

\* Due to unknown MS onset dates, model 4 includes 1632/1822 individuals.

† Time varying covariates.

**Supplementary Table 4: Individuals with prevalent MS and their risk of spasticity treatment for general predictors.**

	Events	PT	M1		M2		M3		M4		M5*		M6		M7	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<b>Sex</b>																
Male	324	6015	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Female	844	17875	0.88	0.77,1.00	0.89	0.78,1.01	0.95	0.83,1.08	0.96	0.84,1.09	0.96	0.84,1.10	0.96	0.84,1.09	0.94	0.83,1.07
<b>Education</b>																
Compulsory	192	2908			1.00		1.00		1.00		1.00		1.00		1.00	
Post-compulsory	532	11036			0.75	0.63,0.89	0.78	0.66,0.92	0.78	0.66,0.92	0.74	0.62,0.88	0.78	0.66,0.92	0.77	0.65,0.92
Tertiary	444	9946			0.71	0.60,0.85	0.76	0.63,0.90	0.76	0.64,0.90	0.72	0.61,0.87	0.76	0.64,0.90	0.75	0.63,0.90
<b>Disease course †</b>																
RRMS	489	14255					1.00		1.00		1.00		1.00		1.00	
PPMS	130	1543					2.77	2.25,3.41	2.70	2.19,3.33	2.68	2.15,3.33	2.73	2.21,3.36	2.72	2.21,3.35
SPMS	519	7360					2.23	1.95,2.56	2.31	2.01,2.66	2.32	2.01,2.69	2.29	1.99,2.62	2.24	1.95,2.58
Unknown	30	732					1.28	0.88,1.85	1.23	0.84,1.78	0.93	0.52,1.66	1.24	0.85,1.79	1.26	0.87,1.83
<b>Age at MS diagnosis</b>	1168	23890							1.02	1.01,1.03						
<b>Age at MS onset</b>	1065	21573									1.01	1.00,1.02				
<b>Years with MS †</b>																
1 to <1.5	2	43											1.00			
>=1.5 to <2	9	119											1.57	0.34,7.32		
>=2 to <2.5	14	187											1.54	0.35,6.82		
>=2 to <3	15	256											1.19	0.27,5.20		
>=3 to <3.5	18	316											1.13	0.26,4.88		
>=3.5 to 4	20	388											0.98	0.23,4.21		
>=4 to <6	113	2414											0.89	0.22,3.61		
>=6 to <8	168	3339											0.92	0.23,3.74		
>=8 to <10	173	3759											0.83	0.20,3.35		
>=10	636	13069											0.79	0.20,3.18		
<b>MS diagnosis year</b>																
1945-1980	47	1092													0.81	0.59,1.12
1981-1990	121	2409													0.89	0.72,1.10
1991-2000	501	9209													1.08	0.95,1.23
2001-2005	499	11179													1.00	

**Abbreviations:** CI=confidence interval; HR=hazard ratio; M=model; RRMS=relapsing remitting MS; PT=person-time; PPMS=primary progressive MS; SPMS; secondary progressive MS.

Individuals with prevalent MS (N=3514) additionally excluding individuals with PPMS/SPMS under age 25 at study entry (n=5). All models adjusted for age and county of residence at MS diagnosis. Disease course and years with MS are time-varying covariates. Reference categories indicated by hazard ratios of 1.00 with no confidence interval.

\* Due to unknown MS onset dates, model 5 includes 3179/3514 individuals.

† Time varying covariates.

**Supplementary Table 5: Sensitivity analysis among incident MS individuals with no diagnosis of depression or prescription for antidepressants. General variables and their association with spasticity treatment.**

	Events	PT	M1		M2		M3		M4 *		M5		M6	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<b>Sex</b>														
Male	78	1725	1.00		1.00		1.00		1.00		1.00		1.00	
Female	169	3815	1.00	0.76,1.32	1.06	0.80,1.39	1.17	0.88,1.55	1.14	0.84,1.54	1.22	0.92,1.63	1.21	0.91,1.61
<b>Education</b>														
Compulsory	27	334			1.00		1.00		1.00		1.00		1.00	
Post-compulsory	120	2612			0.59	0.38,0.92	0.71	0.45,1.11	0.68	0.42,1.09	0.73	0.46,1.16	0.71	0.45,1.13
Tertiary	100	2594			0.49	0.31,0.77	0.57	0.36,0.91	0.61	0.38,1.00	0.60	0.38,0.97	0.57	0.36,0.90
<b>Disease course †</b>														
RRMS	165	4637					1.00		1.00		1.00		1.00	
PPMS	33	200					5.06	3.27,7.82	4.73	3.01,7.43	3.92	2.51,6.12	4.84	3.13,7.48
SPMS	37	363					2.86	1.92,4.25	3.66	2.39,5.59	2.85	1.90,4.27	2.75	1.84,4.10
Unknown	12	340					1.08	0.59,1.96	0.83	0.36,1.89	1.05	0.58,1.93	1.07	0.59,1.95
<b>Age at MS onset</b>	223	5073							1.06	1.03,1.09				
<b>Years with MS †</b>														
<0.5	76	475									1.00			
>=0.5 to <1	29	494									0.42	0.27,0.65		
>=1 to <2	43	983									0.28	0.19,0.42		
>=2 to <3	32	893									0.23	0.15,0.35		
>=3 to <6	54	1912									0.17	0.12,0.25		
>=6	13	782									0.09	0.05,0.18		
<b>MS diagnosis year</b>														
2005	18	624												1.00
2006-2007	95	2229												1.41 0.84,2.37
2008-2009	81	1521												1.87 1.10,3.18
2010-2011	40	920												1.54 0.87,2.73
2012-2014	13	244												1.94 0.93,4.05

**Abbreviations:** CI=confidence interval; HR=hazard ratio; M=model; RRMS=relapsing remitting MS; PT=person-time; PPMS=primary progressive MS; SPMS; secondary progressive MS.

Individuals with incident MS (N=1123) excluding individuals (n=703) ever diagnosed with depression or prescribed an anti-depressant and PPMS/SPMS diagnosed < age 25 year (n=2). All models adjusted for age and county of residence at MS diagnosis. In models where region of residence violated proportional hazards assumption, a stratified Cox model was used. Variable categories with hazard ratios of 1.00 without confidence intervals are reference categories.

\* Due to missing data, model including MS onset includes N=1011.

† Time varying covariates.

**Supplementary Table 6: Sensitivity analysis among incident MS individuals excluding individuals with a history of seizures for general variable associations with spasticity treatment.**

	Events	PT	M1		M2		M3		M4*		M5		M6	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<b>Sex</b>														
Male	131	2462	1.00		1.00		1.00		1.00		1.00		1.00	
Female	308	6586	0.91	0.74,1.12	0.95	0.77,1.18	1.04	0.84,1.28	0.98	0.79,1.22	1.06	0.86,1.31	1.05	0.85,1.30
<b>Education</b>														
Compulsory	55	673			1.00		1.00		1.00		1.00		1.00	
Post-compulsory	219	4323			0.62	0.45,0.84	0.64	0.47,0.87	0.61	0.45,0.85	0.68	0.50,0.93	0.66	0.49,0.90
Tertiary	165	4051			0.50	0.36,0.69	0.53	0.38,0.73	0.56	0.40,0.78	0.56	0.41,0.77	0.54	0.39,0.75
<b>Disease course †</b>														
RRMS	291	7231					1.00		1.00		1.00		1.00	
PPMS	56	413					3.24	2.36,4.45	2.98	2.13,4.16	2.71	1.97,3.74	3.13	2.28,4.30
SPMS	66	729					2.30	1.72,3.07	2.71	2.00,3.68	2.28	1.70,3.05	2.36	1.76,3.15
Unknown	26	674					0.97	0.64,1.45	0.90	0.53,1.52	0.96	0.64,1.44	0.96	0.64,1.44
<b>Age at MS onset</b>	397	8178							1.04	1.02,1.06				
<b>Years with MS †</b>														
<0.5	105	754									1.00			
>=0.5 to <1	46	792									0.46	0.32,0.65		
>=1 to <2	82	1585									0.40	0.30,0.54		
>=2 to <3	60	1444									0.31	0.22,0.42		
>=3 to <6	109	3140									0.25	0.19,0.33		
>=6	37	1333									0.19	0.13,0.28		
<b>MS diagnosis year</b>														
2005	37	1118												1.00
2006-2007	172	3824												1.30 0.91,1.86
2008-2009	138	2355												1.72 1.19,2.49
2010-2011	70	1405												1.52 1.02,2.29
2012-2014	22	346												2.20 1.29,3.77

**Abbreviations:** CI=confidence interval; HR=hazard ratio; M=model; RRMS=relapsing remitting MS; PT=person-time; PPMS=primary progressive MS; SPMS; secondary progressive MS.

Individuals with incident MS (N=1790) excluding individuals ever diagnosed with seizures (n=32) and PPMS/SPMS individuals <= 25 years of age at MS diagnosis (n=4).

Adjusted for age and county of residence at MS diagnosis. In models where region of residence violated the proportional hazards assumption, stratified Cox regression models were used. Variable categories with hazard ratios of 1.00 without confidence intervals are reference categories.

\*Model with MS onset includes N=1605 individuals due to missing onset dates.

† Time-varying covariates.



**Supplementary Table 7: Sensitivity analysis among individuals with prevalent MS with no diagnosis of depression or prescription for antidepressants. General variables and their association with spasticity treatment.**

	Events	PT	M1		M2		M3		M4		M5*		M6		M7	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<b>Sex</b>																
Male	199	4045	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Female	412	10030	0.82	0.69,0.98	0.83	0.70,0.99	0.91	0.77,1.09	0.92	0.78,1.10	0.92	0.77,1.10	0.93	0.78,1.11	0.92	0.77,1.09
<b>Education</b>																
Compulsory	94	1684			1.00		1.00		1.00		1.00		1.00		1.00	
Post-compulsory	279	6382			0.78	0.61,0.99	0.85	0.67,1.08	0.85	0.67,1.08	0.81	0.63,1.05	0.85	0.67,1.09	0.84	0.66,1.07
Tertiary	238	6009			0.72	0.56,0.93	0.78	0.61,1.01	0.78	0.61,1.00	0.76	0.59,0.99	0.79	0.61,1.01	0.78	0.61,1.00
<b>Disease course †</b>																
RRMS	239	8575					1.00		1.00		1.00		1.00		1.00	
PPMS	80	1029					3.27	2.47,4.33	3.20	2.42,4.23	3.20	2.39,4.27	3.22	2.44,4.27	3.25	2.45,4.30
SPMS	273	4034					2.76	2.27,3.36	2.91	2.39,3.55	2.93	2.38,3.62	2.92	2.39,3.56	2.79	2.29,3.40
Unknown	19	437					1.78	1.11,2.86	1.69	1.05,2.73	1.50	0.78,2.86	1.68	1.04,2.71	1.76	1.09,2.83
<b>Age at MS diagnosis</b>	611	14075							1.02	1.01,1.03						
<b>Age at MS onset</b>	559	12768									1.01	1.00,1.02				
<b>Years with MS †</b>																
1 to <1.5	1	26											1.00			
>=1.5 to <2	5	74											1.77	0.20,15.63		
>=2 to <2.5	9	118											1.98	0.24,16.05		
>=2 to <3	12	159											2.11	0.27,16.65		
>=3 to <3.5	10	194											1.30	0.16,10.46		
>=3.5 to 4	12	237											1.12	0.14,8.82		
>=4 to <6	64	1428											1.05	0.14,7.80		
>=6 to <8	99	1960											1.14	0.15,8.37		
>=8 to <10	84	2232											0.80	0.11,5.88		
>=10	315	7646											0.78	0.11,5.74		
<b>MS diagnosis year</b>																
1945-1980	24	673													0.81	0.51,1.26
1981-1990	68	1425													0.92	0.70,1.23
1991-2000	252	5377													1.01	0.84,1.20
2001-2005	267	6599													1.00	

**Abbreviations:** CI=confidence interval; HR=hazard ratio; M=model; RRMS=relapsing remitting MS; PT=person-time; PPMS=primary progressive MS; SPMS; secondary progressive MS.

Individuals with prevalent MS (N=2040) excluding individuals ever diagnosed with depression or prescribed an antidepressant (n=1479) and PPMS/SPMS individuals diagnosed < age 25 years (n=5). All models adjusted for age and county of residence at MS diagnosis. In models where region of residence violated the proportional hazards assumption, a stratified Cox model was used. Categories with HR of 1.00 and no confidence intervals are reference categories.

\* Due to unknown MS onset dates, model 5 includes 1851/2040 individuals.

† Time varying covariates.

**Supplementary Table 8: Sensitivity analysis among individuals with prevalent MS with no diagnosis of seizures. General variables and their association with spasticity treatment.**

	Events	PT	M1		M2		M3		M4		M5*		M6		M7	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<b>Sex</b>																
Male	317	5923	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Female	814	17475	0.87	0.77,0.99	0.89	0.78,1.01	0.94	0.82,1.07	0.95	0.83,1.08	0.96	0.84,1.10	0.95	0.83,1.08	0.94	0.82,1.07
<b>Education</b>																
Compulsory	187	2831			1.00		1.00		1.00		1.00		1.00		1.00	
Post-compulsory	517	10821			0.74	0.63,0.88	0.77	0.65,0.91	0.77	0.65,0.91	0.73	0.61,0.87	0.77	0.65,0.92	0.76	0.64,0.91
Tertiary	427	9746			0.70	0.59,0.84	0.74	0.62,0.89	0.75	0.62,0.89	0.72	0.60,0.86	0.75	0.63,0.89	0.74	0.62,0.89
<b>Disease course †</b>																
RRMS	480	14031					1.00		1.00		1.00		1.00		1.00	
PPMS	121	1497					2.64	2.13,3.27	2.57	2.07,3.19	2.56	2.05,3.20	2.60	2.10,3.22	2.60	2.09,3.22
SPMS	503	7158					2.22	1.93,2.55	2.31	2.01,2.65	2.29	1.97,2.66	2.27	1.98,2.62	2.24	1.94,2.57
Unknown	27	712					1.19	0.80,1.75	1.14	0.77,1.68	0.95	0.53,1.70	1.15	0.78,1.70	1.17	0.79,1.73
<b>Age at MS diagnosis</b>	1131	23398							1.02	1.01,1.03						
<b>Age at MS onset</b>	1034	21142									1.01	1.00,1.02				
<b>Years with MS †</b>																
1 to <1.5	2	42											1.00			
>=1.5 to <2	8	117											1.40	0.30,6.65		
>=2 to <2.5	13	184											1.42	0.32,6.32		
>=2 to <3	15	251											1.18	0.27,5.17		
>=3 to <3.5	18	310											1.13	0.26,4.89		
>=3.5 to 4	20	379											0.98	0.23,4.22		
>=4 to <6	110	2361											0.87	0.21,3.52		
>=6 to <8	160	3269											0.88	0.22,3.56		
>=8 to <10	171	3691											0.81	0.20,3.28		
>=10	614	12794											0.76	0.19,3.04		
<b>Year of MS diagnosis</b>																
1945-1980	46	1053													0.81	0.59,1.12
1981-1990	116	2348													0.88	0.71,1.08
1991-2000	484	9050													1.07	0.94,1.21
2001-2005	485	10947													1.00	

**Abbreviations:** CI=confidence interval; HR=hazard ratio; M=model; RRMS=relapsing remitting MS; PT=person-time; PPMS=primary progressive MS; SPMS=secondary progressive MS.

Individuals with prevalent MS (N=3434) excluding individuals ever diagnosed with seizure (n=80) and PPMS/SPMS individuals <= 25 years of age at study entry (n=5). Adjusted for age and county of residence at MS diagnosis. Disease course and years with MS are time-varying covariates. Reference categories indicated by hazard ratios of 1.00 with no confidence interval.

\* Due to unknown MS onset dates, model 5 includes 3109/3434 individuals.

† Time varying covariates.

**Supplementary Table 9: Expanded disability severity scores as fixed and time-varying covariates, disease course and disease modifying therapies and their association with spasticity treatment among individuals with incident MS.**

Baseline EDSS scores														
EDSS	Events	PT	M1		M2		M3		M4		M5		M6	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
0	15	903	1.00		1.00		1.00		1.00		1.00		1.00	
1-1.5	43	1324	1.78	0.98,3.23	1.70	0.92,3.14	1.62	0.87,3.00	1.61	0.87,2.99	1.47	0.76,2.83	1.47	0.76,2.82
2-2.5	66	1107	3.23	1.83,5.71	3.55	1.97,6.39	3.51	1.95,6.31	3.37	1.88,6.07	2.84	1.52,5.30	2.76	1.48,5.16
3-3.5	39	571	3.63	1.97,6.68	3.64	1.93,6.84	3.48	1.85,6.56	3.27	1.73,6.17	2.67	1.33,5.37	2.63	1.31,5.29
4+	31	266	6.18	3.25,11.75	5.39	2.75,10.56	5.68	2.90,11.15	4.54	2.29,9.03	3.98	1.83,8.64	3.82	1.75,8.31
<b>Age at onset</b>	405	8325			1.05	1.02,1.07	1.05	1.02,1.08	1.07	1.04,1.10	1.03	1.00,1.06	1.03	1.00,1.06
<b>Disease course</b>														
RRMS	312	7540							1.00		1.00		1.00	
PPMS	57	417							1.71	0.97,3.02	1.07	0.44,2.56	1.11	0.46,2.65
SPMS	53	569							2.88	1.77,4.66	2.26	1.26,4.05	2.15	1.19,3.87
Unknown	26	694							0.46	0.17,1.27	0.61	0.19,1.96	0.61	0.19,1.96
<b>DMT<sup>†</sup></b>														
None	29	1144									1.00		1.00	
Mod effective	266	6443									1.59	0.88,2.86	1.78	0.97,3.25
High effective	40	643									1.90	0.94,3.84	2.18	1.06,4.50
Time varying EDSS scores														
EDSS <sup>‡</sup>	Events	PT	TVC1		TVC2		TVC3		TVC4		TVC5		TVC6	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
No score	16	1076	1.00		1.00		1.00		1.00		1.00		1.00	
0	27	1605	1.18	0.64,2.20	1.35	0.69,2.63	1.37	0.70,2.68	1.44	0.74,2.80	2.64	1.13,6.17	3.24	1.37,7.62
1.0-1.5	56	2161	1.78	1.01,3.12	1.85	1.01,3.38	1.85	1.01,3.39	1.93	1.05,3.53	3.20	1.43,7.17	3.95	1.77,8.81
2.0-2.5	81	1641	3.23	1.87,5.58	3.47	1.92,6.26	3.45	1.91,6.22	3.48	1.93,6.26	5.69	2.59,12.49	7.03	3.19,15.50
3.0-3.5	57	922	4.04	2.27,7.19	4.35	2.33,8.14	4.28	2.28,8.02	4.27	2.28,7.99	7.65	3.38,17.29	9.25	4.11,20.82
4.0-4.5	27	306	5.92	3.13,11.20	7.03	3.61,13.69	6.99	3.58,13.64	6.44	3.28,12.66	10.92	4.46,26.77	13.30	5.46,32.38
5.0-5.5	13	123	6.80	3.16,14.61	8.11	3.33,19.71	7.93	3.21,19.60	6.92	2.78,17.25	11.79	4.02,34.61	15.96	5.70,44.66
6.0-8.5	45	259	11.31	6.15,20.79	11.20	5.72,21.94	11.00	5.61,21.59	9.84	5.00,19.35	14.14	5.44,36.76	18.63	7.23,48.00
<b>Age at onset</b>	302	7528			1.04	1.02,1.07	1.04	1.02,1.07	1.05	1.03,1.07	1.04	1.02,1.07	1.02	1.00,1.05
<b>Disease course</b>														
RRMS	235	6802							1.00		1.00		1.00	
PPMS	38	358							1.45	0.90,2.33	1.10	0.56,2.15	1.19	0.62,2.25
SPMS	40	541							1.81	1.22,2.70	1.46	0.93,2.29	1.35	0.87,2.11
Unknown	9	391							0.59	0.27,1.27	0.59	0.25,1.44	0.59	0.24,1.45
<b>DMT<sup>†</sup></b>														
None	27	1055									1.00		1.00	
Mod effective	199	5796									1.22	0.76,1.97	1.47	0.92,2.35
High effective	34	599									1.55	0.85,2.85	1.91	1.04,3.51

**Abbreviations:** CI=confidence interval; High=highly; HR=hazard ratio; M=model; Mod=moderately; RRMS=relapsing remitting MS; PT=person-time; PPMS=primary progressive MS; SPMS; secondary progressive MS; TVC=time-varying covariate.

Individuals with incident MS. Model 1 adjusted for age, county of residence at MS diagnosis, and highest attained education. Model 2 additionally adjusted for number of years from MS onset to diagnosis and calendar year of MS diagnosis. Model 3 additionally adjusted for vascular disease and depression. Model 6 additionally adjusted for time with MS as an additional timescale. Note, due to missing values, the number of individuals in each model vary. Baseline EDSS: Model 1 N=811, Models 2-4 N=764, Models 5-6 N=670. Time-varying EDSS: TVC 1 N=1510, TVC 2-4 N=1398, and TVC 5-6 N=1258. More individuals were included in the TVC EDSS models as not all had baseline EDSS scores, but were assessed for their EDSS scores after baseline. <sup>†</sup> Time-varying covariates.

**Supplementary Table 10: Comorbid diseases as risk factors for spasticity treatment among individuals with incident and prevalent MS.**

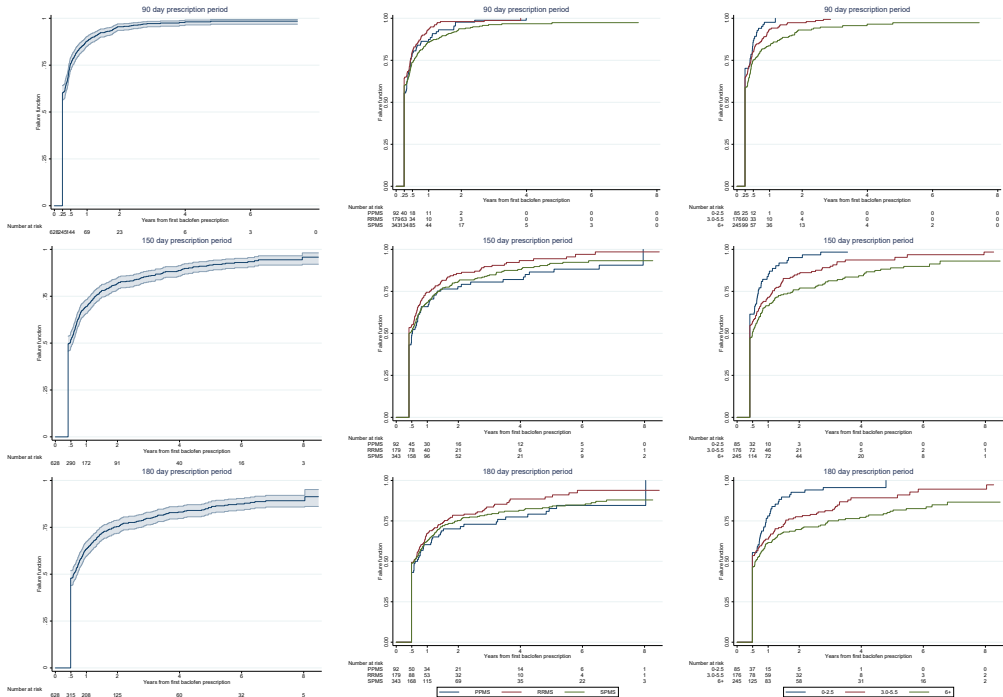
<i>Incident MS (N=1822)</i>	Events	PT	M1		M2		M3	
			HR	95% CI	HR	95% CI	HR	95% CI
<b>Concussion or TBI*</b>			/	/	/	/	/	/
<b>Coronary artery disease</b>	3	25	2.04	0.83,4.98	2.17	0.86,5.43	2.83	1.12,7.18
<b>Depression</b>	198	2878	1.66	1.37,2.01	1.59	1.31,1.93	1.83	1.50,2.23
<b>Diabetes</b>								
Type I	5	17	3.06	1.32,7.11	2.73	1.17,6.34	2.68	1.12,6.39
Type II/Unknown	2	59	0.58	0.18,1.83	0.53	0.16,1.69	0.60	0.19,1.93
<b>Parkinson's disease</b>	2	10	3.20	1.47,6.94	3.61	1.65,7.89	3.55	1.62,7.75
<b>Seizure</b>	9	147	1.47	0.75,2.87	1.52	0.78,2.98	1.68	0.86,3.30
<b>Stroke</b>	3	83	0.80	0.35,1.81	0.88	0.38,2.01	0.91	0.40,2.10
<b>Vascular disease</b>	16	123	2.02	1.31,3.12	2.09	1.34,3.27	2.32	1.48,3.64
<hr/>								
<i>Prevalent MS (N=3514)</i>								
<b>Concussion or TBI</b>	5	54	1.73	0.86,3.51	1.47	0.73,2.98	1.48	0.73,2.99
<b>Coronary artery disease</b>	15	239	1.20	0.80,1.79	1.20	0.80,1.80	1.22	0.81,1.83
<b>Depression</b>	544	7885	1.76	1.56,1.97	1.72	1.53,1.94	1.74	1.55,1.95
<b>Diabetes</b>								
Type I	2	56	1.14	0.54,2.41	1.25	0.59,2.64	1.26	0.60,2.65
Type II / Unknown	8	164	0.87	0.53,1.44	0.83	0.50,1.36	0.83	0.51,1.37
<b>Parkinson's disease</b>	8	94	1.46	0.95,2.26	1.41	0.91,2.18	1.41	0.91,2.18
<b>Seizure</b>	37	369	2.06	1.48,2.87	1.87	1.35,2.61	1.89	1.36,2.63
<b>Stroke</b>	19	351	1.30	0.93,1.80	1.34	0.96,1.87	1.34	0.96,1.86
<b>Vascular disease</b>	42	845	1.23	0.99,1.54	1.20	0.96,1.50	1.21	0.97,1.51

**Abbreviations:** CI=confidence interval; HR=hazard ratio; M=model; PT=person-time; TBI=traumatic brain injury.

All risk factors for spasticity were used as time-varying covariates and models included each risk factor individually. Reference categories are individuals without the comorbid disease.

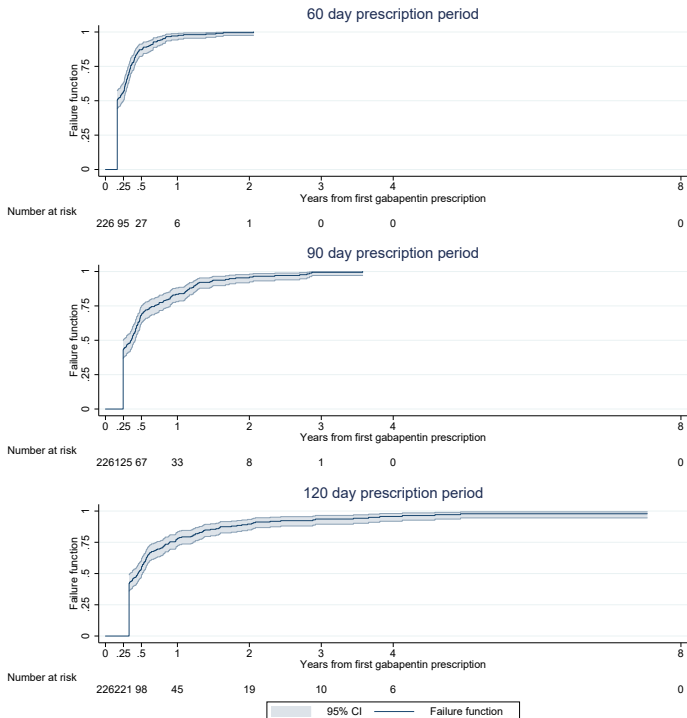
Model 1 adjusted for age, county of residence at MS diagnosis, and highest attained education. Model 2 additionally adjusted for disease course as a time-varying covariate. Model 3 additionally adjusted for years with MS as an additional timescale. Stratified Cox regression models were used in the incident MS cohort where region of residence did not meet the proportional hazards assumption and among the prevalent MS cohort where education did not meet proportional hazards assumption. Additional incident MS individuals (n=4) at MS diagnosis and prevalent MS individuals (n=5) at study entry with PPMS/SPMS ≤ 25 years of age were excluded.

\*Concussion or TBI estimates could not be computed as few individuals experienced concussion or TBI.

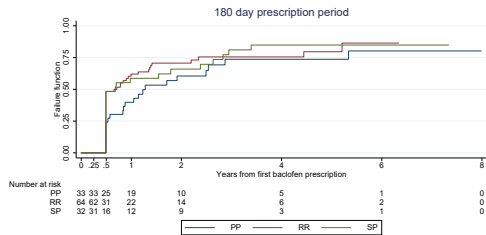
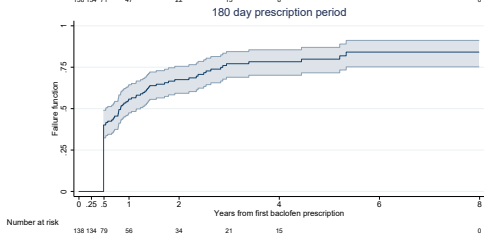
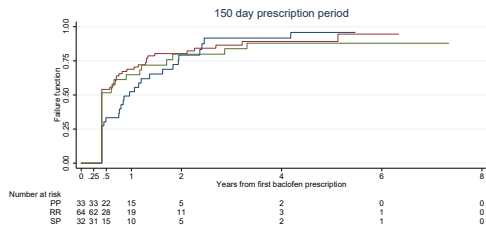
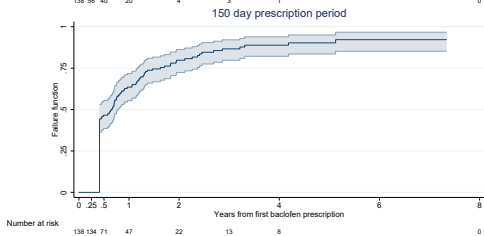
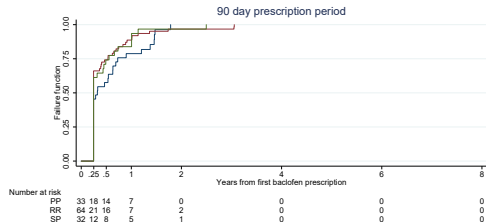
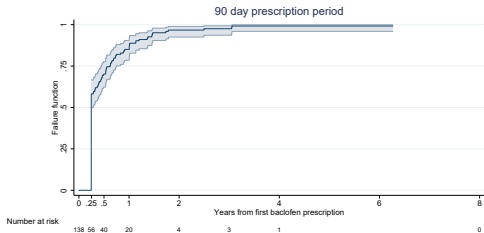


Supplementary Figure 1: Time to discontinuation of baclofen among people with prevalent multiple sclerosis stratified by disease course and Expanded Disability Severity Scale (EDSS). Left column, overall discontinuation. Middle column, discontinuation stratified by disease course when starting baclofen. Right column, discontinuation stratified by EDSS score when starting baclofen. Abbreviations: RRMS = Relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis.





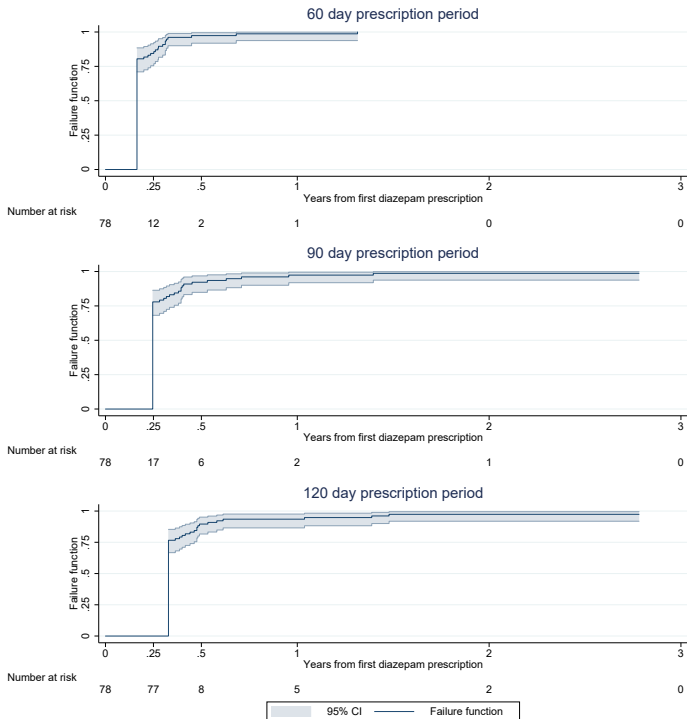
Supplementary Figure 4: Time to discontinuation of gabapentin among people with incident multiple sclerosis who had gabapentin as their first drug to treat possible spasticity.



Supplementary Figure 4: Time to discontinuation of baclofen of people who first had baclofen prior to any other spasticity treatment among people with incident multiple sclerosis stratified by disease course.

Left column, overall discontinuation. Right column, discontinuation stratified by EDSS score when starting baclofen.

Abbreviations: RR = Relapsing-remitting multiple sclerosis; SP = secondary progressive multiple sclerosis; PP = primary progressive multiple sclerosis.



Supplementary Figure 4: Time to discontinuation of diazepam among people with incident multiple sclerosis who had diazepam as their first drug to treat possible spasticity.