

Retention of antiseizure medications for epilepsy in multiple sclerosis: A retrospective observational study

Zamzam Mahamud^a, Samuel Håkansson^a, Joachim Burman^b, Johan Zelano^{a,c,*}

^a Department of Clinical Neuroscience, Sahlgrenska Academy, University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden

^b Department of Neuroscience, Uppsala University, Uppsala, Sweden

^c Wallenberg Centre for Molecular and Translational Medicine, Sahlgrenska Academy, Gothenburg, Sweden

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ABSTRACT

Purpose: Epilepsy in multiple sclerosis (MS) is rare, and longitudinal clinical studies evaluating treatment with antiseizure medications (ASMs) are difficult to conduct. We instead designed a nationwide register study to estimate retention rates of ASMs prescribed as initial monotherapy for epilepsy in MS and investigated factors influencing their retention.

Methods: multiple sclerosis patients with a first prescription of ASM for epilepsy were identified by cross-referencing the Swedish MS register with comprehensive national registers. One and five-year retention rates of ASMs were estimated using Kaplan–Meier analysis. Cox proportional regression was employed to estimate hazard ratios (HR) of discontinuation for different ASMs as well as for baseline predictors. **Results:** One hundred and twenty-nine MS patients were included. The most commonly prescribed ASMs were: carbamazepine ($n = 38$, 29.5%), lamotrigine ($n = 33$, 25.6%) and levetiracetam ($n = 19$, 14.7%). One-year retention rates (95% CI) were: lamotrigine 87.5% [76, 98.9], carbamazepine 60.5% [45, 76], levetiracetam 60.2% [37.2, 83.2], valproate 51.3% [23, 79.6] and phenytoin 44.4% [11.8, 77]. Five-year retention rates (95% CI) were: lamotrigine 74.4% [57.3, 91.5], carbamazepine 52.2% [34.9, 69.4], valproate 51.3% [23.1, 79.5] and phenytoin 14.8% [0, 40.9]. With carbamazepine as reference, lamotrigine was the only ASM that displayed a lower hazard of discontinuation, HR 0.41 [0.17, 0.99]. We could not identify any baseline factors that influenced the risk of discontinuation.

Conclusion: Lamotrigine displayed the lowest risk of discontinuation when prescribed as initial monotherapy for epilepsy in MS. Newer ASMs generally compared well to older ones, at least suggesting non-inferiority.

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1. Introduction

Multiple sclerosis (MS) is a severe demyelinating disease of the central nervous system. Sometimes it is complicated by epileptic seizures, and the prevalence of epilepsy in MS has been estimated to be 3% [1]. When treated with antiseizure medications (ASMs), one-year seizure freedom in MS ranges from approximately 20–80% [2–5]. The great variance in seizure freedom could be explained by small study sizes and sampling differences, but differences in the choice of ASM treatment could also have influenced rates of seizure freedom.

There is no robust evidence to guide ASM selection for treatment of epilepsy in MS as most studies have been small and

descriptive in nature [6]. However, since the prevalence of MS is low and concomitant epilepsy is infrequent, study cohorts of considerable size and follow-up would be needed for longitudinal clinical studies making them not really feasible [7]. Registers can provide an alternative to clinical studies and have been used previously to estimate retention rates of ASMs [8]. The retention rate is a composite measure of the efficacy and tolerability of an ASM and is frequently used to assess treatment outcome [9]. In a recent Swedish study using patient records, a trend of higher retention rates was noted for newer ASMs used for epilepsy in MS compared to older ones, although the differences were not statistically significant. The most common reason for discontinuation was side effects [3]. We used nationwide Swedish registers to test the hypothesis that newer ASMs have higher retention rates than older ASMs when prescribed as initial monotherapy in MS. We also aimed to investigate baseline factors that could predict discontinuation of the initial ASM.

* Corresponding author at: Department of Clinical Neuroscience, Sahlgrenska Academy, University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden.

E-mail address: johan.zelano@neuro.gu.se (J. Zelano).

2. Materials and methods

2.1. Study design and registers

This was a retrospective register-based study. Patients were selected from the Swedish MS register (SMSreg), a nationwide register which was established in 1998. At the time of data export and end of study (31st December 2014), SMSreg included 15,810 patients. Demographic and MS-specific data were obtained from SMSreg. Data on seizure-related diagnoses were obtained from the National Patient Register (NPR). Date of death was extracted from the Cause-of-Death Register (CDR). Both the NPR, which includes all inpatient diagnoses since 1987 and all outpatient diagnoses since 2005, and the CDR, which was established in 1961, are obligatory to report to for healthcare providers in Sweden. The Drug Register (DR) contains data on all dispensations of prescription drugs made in Swedish pharmacies since 1st July 2005. From the DR we extracted all dates of prescription and dispensation for drugs with ATC-code N03, i.e., antiepileptics.

2.2. Definitions

Epilepsy was defined as ICD-9 code 345 except 345Q or ICD-10 G40. Seizure was defined as ICD-9 780D and 345Q or ICD-10 R56.8 and G41. In the analyses, “old ASM” denoted first generation ASMs and included: carbamazepine, clonazepam, phenytoin, and valproate. “New ASM” denoted second and third generation ASMs and included: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, and vigabatrin.

2.3. Study cohort

We included patients who had received epilepsy diagnosis after MS onset and who were prescribed ASM monotherapy at treatment start (Fig. 1). In order to identify the initial ASM after epilepsy onset, only MS patients with epilepsy diagnosis after the start of the DR, i.e., 1st July 2005, were included. Also, patients were

required to have received their first ASM prescription after their first code for seizure or epilepsy to increase the likelihood of the ASM being used for its anti-seizure properties as opposed to for pain or paroxysmal symptoms which are also common indications for ASMs in MS [10].

2.4. Statistical analyses

Descriptive data are presented as absolute numbers and percentages or mean with standard deviation (SD). Kaplan–Meier analysis was used to estimate retention rates of the initial ASMs and Cox regression was used to compare risks of discontinuation between ASMs. In the analyses, patients were stratified according to their initial ASM and followed up from the first dispensation to treatment end (event), death or study end (31st December 2014), whichever occurred first. Treatment end was defined as the elapse of at least a year without a new dispensation or change to another ASM and dated as three months after the final dispensation since prescription refill interval in Sweden is typically three months. Only ASMs with at least 10 users were included into the analyses. Retention rates were estimated after one and five years of follow-up and 95% confidence intervals (CIs) were calculated as the standard error (SE) multiplied by 1.96. Hazard ratios (HR) of discontinuation for ASMs were estimated for up to five years of follow-up. We also used Cox regression to assess the impact of available baseline variables on the risk of discontinuation of the initial ASM. In this analysis, the entire available follow-up period was modeled. Analyses were carried out in SPSS version 24 (IBM Corp., Armonk, N.Y., USA) and GraphPad QuickCalcs (<https://www.graphpad.com/quickcalcs/>).

2.5. Ethical approval

This study was approved by regional ethics committee of Gothenburg (186–15). Upon enrollment into SMSreg, patients consented to their data being used for research.

2.6. Data availability statement

Data sharing agreements with the register holders prevent the authors from sharing the data sets. For access to the original data, the register holders should be contacted directly.

3. Results

3.1. Demographics and clinical characteristics

The prevalence of epilepsy in the whole register cohort was 3.5%. We included a total of 129 patients with MS and epilepsy (Fig. 1). The majority were female (67.4%) and had progressive forms of MS (69.7%). The average time from epilepsy diagnosis to first prescription of ASM was -0.3 ± 1.57 years (Table 1). Prescription of ASM on seizure indication was significantly more common before compared to after epilepsy diagnosis ($n = 84$ before vs 45 after, $p = 0.001$).

3.2. Choice of ASM at first prescription and subsequent retention

The likelihood of being prescribed a new AED at treatment start increased the later the year of MS onset. For the entire study period however, the proportions of older and newer ASMs prescribed at treatment start were more or less equal (49% vs 51% respectively, $p = 0.914$). There were no significant differences between patients who received old and new ASMs regarding age, sex, or MS subtype at treatment start. Carbamazepine was the most commonly pre-

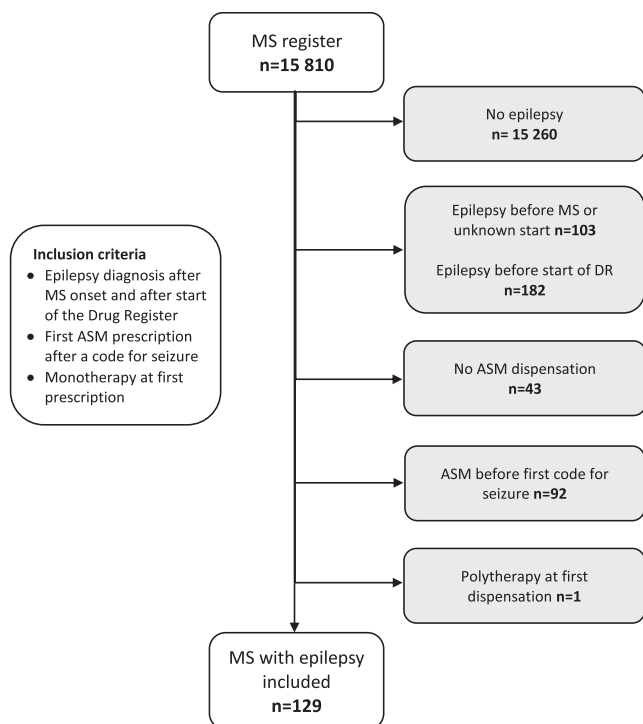


Fig. 1. Flow diagram of inclusion and exclusion of patients.

Table 1
Demographics and clinical characteristics at export.

Variable	n (%) or $\bar{x} \pm SD$
Sex	n = 129
Female	87 (67.4%)
Male	42 (32.6%)
Age at MS onset (y)	31.8 ± 12.2
MS course	
PPMS	13 (10%)
PRMS	3 (2.3%)
RRMS	36 (27.9%)
SPMS	74 (57.4%)
Missing	3 (2.3%)
Time from MS onset to epilepsy (y)	18.4 ± 12.2
Time from first code for seizure to first ASM prescription (y)	1.24 ± 2.9
Time from epilepsy to first ASM prescription (y)	-0.3 ± 1.57

Abbreviations: ASM, Antiseizure medication; MS, Multiple sclerosis; PPMS, Primary progressive MS; PRMS, Primary progressive MS; RRMS, Relapsing-remitting MS; SPMS, Secondary progressive MS.

scribed initial ASM (29.5%), followed by lamotrigine (25.6%) and levetiracetam (14.7%) (Table 2). A total of four (3.1%) patients were treated with an additional ASM, two received levetiracetam and two received gabapentin. Of the 44 (34.1%) patients that changed ASM, the most common choices were lamotrigine (n = 12, 27.2%) and levetiracetam (n = 10, 22.7%). Of the 13 prescribed valproate, 6 (46.2%) were women, often above child bearing age (median age 44.5 years, range 27–62).

3.3. Risk of discontinuation

In Kaplan–Meier analysis, lamotrigine had the highest retention rates with estimates of 87.5% [95% CI 76, 98.9] at one year and 74.4% [95% CI 57.3, 91.5] at five years (Fig. 2, Table 3). It was followed by carbamazepine with 60.5% [95% CI 45, 76] at one year and 52.2% [95% CI 34.9, 69.4] at five years. Retention rate for levetiracetam was 60.2% [95% CI 37.2, 83.2] at one year, but observation time was too short to estimate it at five years. Retention of valproate at one year was 51.3% [95% CI 23, 79.6] and remained the same at five years. Phenytoin had the lowest retention rates, 44.4% [95% CI 11.8, 77] at one year and 14.8% [95% CI 0, 40.9] at five years.

In a Cox proportional hazard model with carbamazepine as reference, discontinuation of lamotrigine was significantly less likely, HR 0.41 [0.17, 0.99]. No other ASM had a significantly lower HR of discontinuation compared to carbamazepine (Table 3).

3.4. Effect of baseline characteristics on discontinuation

We investigated the impact of age, sex, new ASM, and MS subtype on the hazard of discontinuation of the initial ASM, but none significantly impacted the risk of discontinuation (Table 4).

Table 2
Frequencies of ASM choice at first prescription, subsequent add-on, and change.

First ASM	n = 129	Mean follow up (years)	Monotherapy throughout	Received add-on	Changed ASM
CBZ	38	3.2 ± 1.5	20 (52.6%)	3 (7.9%)	15 (39.5%)
LTC	33	3.7 ± 2.5	28 (84.8%)		5 (3.0%)
LEV	19	1.4 ± 1.3	14 (73.7%)		5 (26.3%)
VPA	13	3.4 ± 3.7	5 (38.5%)	1 (7.7%)	7 (53.8%)
PHT	10	1.5 ± 1.9	4 (40.0%)		6 (60%)
GAB	8	1.8 ± 2.6	5 (62.5%)		3 (37.5%)
OXC	3	1.7 ± 0.5	2 (66.7%)		1 (33%)
CLZ	2	1.7 ± 2.0	2 (100%)		0 (0%)
PGB	2	1.8 ± 0.1	1 (50%)		1 (50%)
VGB	1	6.7	0 (0%)		1 (100%)

Abbreviations: ASM, Antiseizure medication; CBZ, Carbamazepine; CLZ, Clonazepam; GAB, Gabapentin; LEV, Levetiracetam; LTC, Lamotrigine; OXC, Oxcarbazepine; PGB, Pregabalin; PHT, Phenytoin; VGB, Vigabatrin; VPA, Valproate.

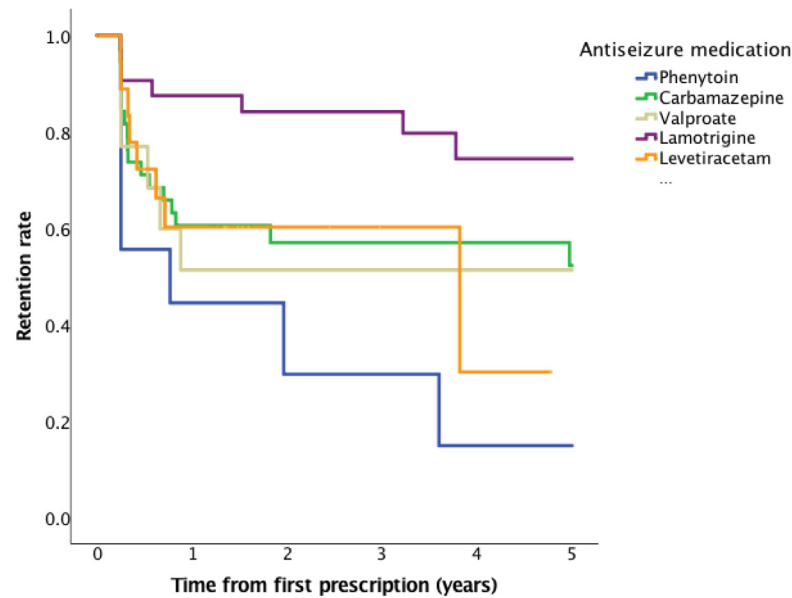
4. Discussion

In this study, we described initial ASM monotherapy in newly diagnosed epilepsy in MS and presented retention rates of the initial ASMs as well as the effect of baseline factors on their retention. We found carbamazepine and lamotrigine to be the most common choices at treatment start but discontinuation to be significantly less common on lamotrigine. We did not find any baseline variable that could predict discontinuation of the initial ASM.

According to the International League Against Epilepsy, retention rates of ASMs from RCTs after a follow-up of at least 48 weeks provide a reliable measure for assessing ASM efficacy and tolerance [9]. High-quality clinical trials of adequate size and sufficient follow-up are however few, and hitherto non-existing for MS [7]. Registers, when comprehensive, are a good alternative to clinical trials with the added advantage of being able to pool patients from different centers in a way that is more cost effective and easier for the patients [11]. This is especially advantageous in studying rare outcomes in diseases that already have a low prevalence such as epilepsy in MS. Furthermore, registers allow for extended periods of observation of study persons. Given the dynamic and progressive nature of MS, longer observation time may be crucial for a more comprehensive understanding of ASM response in this patient group.

Retention rates of ASMs for epilepsy in MS have been estimated previously, although with slightly different results from ours. For example, with a median follow-up of eight years, Dagiasi et al. reported that levetiracetam had the highest retention rate at 100%, while lamotrigine only attained a retention rate of 50%. The retention rate reported for carbamazepine was similar to ours, while no patient continued with valproate at last follow-up in their study [3]. Cohort size and slight differences in methods could have contributed to the discrepancies, however it is also likely that a lack of standardization of indications for ASMs in MS, and hence differences in patient cohorts, could have been an important factor. So far, there is no consensus on whether patient factors, such as MS subtype or type of MS therapy, in addition to seizure classification should be considered when selecting ASM treatment. In our analyses, we did not find any association between baseline variables such as MS subtype and discontinuation of the initial ASM in general. Our material was however too small for subgroup analyses of individual ASMs. The effects of baseline patient characteristics, as well as clinical parameters that could influence discontinuation, for example, EEG readings [12], should be assessed for individual ASMs in a larger material to be able to draw decisive conclusions.

Side effects is the most common cause of ASM discontinuation in MS patients with epilepsy [3]. According to a recent review, no significant interactions had been reported between newer ASMs and disease modifying drugs used in MS while interactions were common with older ASMs [13]. Older ASMs have also been



	Numbers at risk					
Carbamazepine	38	23	15	13	13	11
Lamotrigine	33	26	25	19	12	10
Levetiracetam	19	10	4	2	1	0
Valproate	13	6	6	5	5	4
Phenytoin	10	4	2	2	1	1
Total	113					

Abbreviations: ASM, Antiseizure medication

Fig. 2. Survival adjusted retention of the first prescribed ASM.

Table 3
Retention rates and crude hazard ratios (HR) of discontinuation of the initial ASM.

ASM	One-year retention rate % [95% CI]	Five-year retention rate % [95% CI]	HR [95% CI]
Carbamazepine	60.5 [45,76]	52.2 [34.9, 69.4]	reference
Lamotrigine	87.5 [76, 98.9]	74.4 [57.3, 91.5]	0.41 [0.17, 0.99]
Levetiracetam	60.2 [37.2, 83.2]	-	1.11 [0.47, 2.62]
Valproate	51.3 [23, 79.6]	51.3 [23.1, 79.5]	1.11 [0.44, 2.81]
Phenytoin	44.4 [11.8, 77]	14.8 [0, 40.9]	0.46 [0.19, 1.12]

Abbreviations: ASM, Antiseizure medication.

reported as having significant drug-disease interactions in MS. For example, the action of sodium channel blockers such as carbamazepine on already compromised demyelinated axons can give rise to symptoms that mimic MS relapse [14]. Despite this, almost a third of patients in our sample were prescribed carbamazepine at treatment start. Overall, carbamazepine was the most commonly prescribed ASM for newly diagnosed epilepsy in Sweden during the period of study [15]. In MS, this could reflect the fact that focal seizures, often with secondary generalization, are the most commonly reported seizure types in MS [16–18]. Furthermore, older ASMs have often been used for management of other MS complications, such as carbamazepine for trigeminal neuralgia [10], and may thus be preferred.

It has been proposed that the side-effect profile of an ASM is of greater consequence than its efficacy for predicting the retention rate [19]. Since response to ASM treatment in MS has generally been described as good [16,20], we had expected to find higher retention rates among newer ASMs compared to older ones. In this

Table 4
Crude hazard ratios (HR) of the effect of baseline factors on discontinuation of first ASM.

	HR [95% CI]
Age at MS onset	1.00 [0.97, 1.02]
Age at first seizure	1.00 [0.97, 1.02]
Age at epilepsy diagnosis	0.99 [0.97, 1.02]
Male	0.70 [0.37, 1.29]
New ASM	0.60 [0.34, 1.04]
PPMS	1.46 [0.62, 3.44]
RRMS	0.93 [0.51, 1.68]
SPMS	0.89 [0.50, 1.56]

Abbreviations: ASM, Antiseizure medication; MS, Multiple sclerosis; PPMS, Primary progressive MS; PRMS, Primary progressive MS; RRMS, Relapsing-remitting MS; SPMS, Secondary progressive MS.

study, retention rate was highest for lamotrigine, but the hazard of discontinuation of older and newer ASMs did not differ on group

level. This at least indicates non-inferiority of newer ASMs. Exposure time to newer ASMs was however limited in our study and longer exposure, as well as larger patient samples to capture more ASMs as ours mainly contrasted carbamazepine and lamotrigine, are needed to draw firm conclusions. Nevertheless, a recent review including comments from a consensus exercise with experts in MS and epilepsy, respectively, was in favor of newer ASMs for epilepsy in MS due to fewer side effects [13].

In our study, more patients were prescribed their first ASM before compared to after an actual epilepsy code. This could simply be an administrative artifact due to delayed coding of epilepsy. However, it could also indicate a practice among some clinicians of prescribing ASMs after a single seizure in MS since underlying severe brain disease is known to be associated with increased risk of seizure recurrence [21]. We have previously shown that the risk of epilepsy after a single seizure in relapsing-remitting MS does not differ significantly from that of the general population, but that patients with secondary progressive MS may have a substantially increased risk of seizure recurrence that could warrant early diagnosis and treatment [22].

There are limitations to this study. We used non-randomized retrospective data from registers. Non-randomization when comparing efficacy and tolerability of drugs may introduce systematic bias if drugs are prescribed differently depending on patient characteristics. For instance, clinicians may have avoided carbamazepine in patients that were perceived susceptible to ataxia or fatigue. We attempted to investigate this and found no significant differences in age, sex, and MS subtype in patients prescribed new and old ASMs at treatment start. Paroxysmal symptoms in MS can at times be mistaken for focal seizures and are often also treated with ASMs, hence this could have been a source of confounding. Reassuringly, the accuracy of epilepsy codes in MS in the NPR has been estimated at 94% [3]. ASM prescription data were only available from 1st July 2005, so in order to capture the first ASM we only included patients with epilepsy diagnosis after this date. As a result, this cohort had a longer mean interval between MS onset and epilepsy diagnosis than previously observed [23]. This might affect the generalizability of our results. However, our approach provides the largest study on retention rates of ASMs in MS thus far which might balance out any potential loss of precision. Still, for some ASMs, the number of included patients was low leading to wide confidence intervals which may make comparison difficult. Retention rates of ASMs in MS should be estimated in larger materials, preferably in countries with larger administrative databases, to provide more precise estimates. Furthermore, the registers provided no information on seizure freedom rates, nor reasons for discontinuation. This could have been valuable information in understanding the reasons for high versus low retention. We also lacked information on dosage of the ASMs which could be important for examining whether therapeutic dosages were used and hence evaluating clinical relevance of our findings.

5. Conclusion

We found lamotrigine to be associated with the lowest risk of discontinuation when prescribed as initial monotherapy for epilepsy in MS. Considering the more favorable side-effect profiles of newer ASMs, lamotrigine should be considered more often as initial ASM monotherapy for epilepsy in MS.

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Declaration of Competing Interest

J. Zelano reports consultancy fee from the Swedish medical products agency, the National Board of Health and Welfare and speaker honoraria from UCB and Eisai for non-branded educational events. As an employee of Sahlgrenska university hospital (no personal compensation) he is/has been investigator in clinical trials sponsored by GW pharma, Bial, SK life science, and UCB. The other authors have no disclosures to report.

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