Acquired epilepsy in multiple sclerosis

A nationwide register-based investigation into prognosis and treatment

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To people with multiple sclerosis

ABSTRACT

The prevalence of epilepsy in persons with multiple sclerosis (MS) is thrice that of the general population. The association between epilepsy and MS prognosis and its management are however largely unknown. The prevalence of concomitant MS and epilepsy is low, making recruitment of sufficient numbers of patients for single-centre studies difficult. To circumvent this, we cross-referenced the Swedish MS register (SMSreg), which covers at least 80% of prevalent MS cases, with a series of other national registers, making a cohort of up to 370 MS patients with epilepsy available for our studies. This thesis addresses clinically pertinent questions on diagnosis, prognostic impact and treatment of epilepsy in MS.

In a first-ever evaluation, we found the 10-year risk of epilepsy following a first unprovoked seizure in MS to be 51.4% (95% CI 44 – 58.9%). Hence, a single seizure in MS is not sufficient for epilepsy diagnosis as it does not exceed the diagnostic threshold (60%) (Paper I). In assessing the prognostic impact of epilepsy, we found epilepsy to be associated with at least fourfold increased mortality, although seizure-related deaths were rare. Epilepsy was not associated with an increased risk of conversion to secondary progressive MS (Paper II). Regarding treatment of epilepsy in MS, we discovered carbamazepine to be the most prescribed antiseizure medication at treatment initiation, although retention tended to be higher with lamotrigine (Paper III). Lastly, we tested the hypothesis whether the introduction of disease modifying treatments for MS has affected the incidence of epilepsy in MS. We could not confirm this, but instead found a steady increase in epilepsy prevalence between 1991 – 2018 (Paper IV).

In conclusion, we confirm a negative prognostic association between epilepsy and MS and offer novel insights into diagnosis and treatment of epilepsy in MS. We also demonstrate the feasibility and necessity of using a register-based approach to study a relatively rare form of acquired epilepsy.

Keywords: Multiple sclerosis, epilepsy, seizure, diagnosis, mortality, antiseizure medication, prevalence, incidence

SAMMANFATTNING

Epilepsi är ungefär trippelt så vanligt bland patienter med multipel skleros (MS) jämfört med normalbefolkningen. Förvärvad epilepsi, dvs. epilepsi som uppkommer sekundärt till annan sjukdom, är generellt förenad med ökad dödlighet och försämrad prognos, men betydelsen av epilepsi för MS prognos är föga utforskad. En viktig begränsande faktor har varit den låga prevalensen av samtidig MS och epilepsi som försvårat rekryteringen av tillräckligt många studiepersoner. Genom samkörning av det svenska MS registret och andra nationella register identifierade vi ca 370 MS patienter med epilepsi, vilket är en av de största kohorterna som studerats hittills. Avhandlingens mål var att förbättra kunskapsläget om och behandlingen av epilepsi vid MS, och den innefattar fyra registerbaserade studier som undersöker diagnostisering, prognostisk betydelse och optimal behandling av epilepsi vid MS.

År 2014 reviderades den kliniska definitionen av epilepsi så att diagnosen kan ställas redan efter ett första anfall hos patienter med hög risk för nytt anfall (minst 60%). Risken för ett andra anfall hos MS patienter var då okänd. I avhandlingens första studie uppskattade vi denna risk till 51,4% (95% CI 44 – 58,9%) inom 10 år, och således stödjer inte våra resultat att enbart MS-diagnos är tillräcklig för epilepsidiagnos redan efter att första anfall.

Beträffande betydelsen av epilepsi för MS prognos fann vi ingen koppling mellan epilepsi och övergång till det svårare sjukdomsstadiet sekundärprogressiv MS. En epilepsidiagnos var dock förknippad med minst fyrdubblad ökad risk för död, och vi bekräftar således att förvärvad epilepsi även vid MS är en negativ prognostisk markör.

I frågan om optimal behandling fann vi att lamotrigin var det antiepileptikum som MS patienter tenderade att kvarstå längst på men att det äldre karbamazepin var det vanligaste valet vid nyförskrivning. Våra resultat stödjer därför att nyare antiepileptika med mindre biverkningar skulle kunna vara lämpligare val för epilepsi vid MS. Vi undersökte även om användandet av alltmer effektiva sjukdomsmodifierande läkemedel för MS åren 1991 – 2018 var förknippat med en sjunkande förekomst av epilepsi men fann inget sådant samband.

Sammanfattningsvis är epilepsi vid MS en negativ prognostisk markör. Avhandlingen ger vägledning i frågor rörande dess diagnostisering och behandling, vilka hittills varit outforskade.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Mahamud Z**, Burman J, Zelano J. Risk of epilepsy after a single seizure in multiple sclerosis. *European journal of neurology* 2018;25:854-860.

II. **Mahamud Z**, Burman J, Zelano J. Prognostic impact of epilepsy in multiple sclerosis. *Mult Scler Relat Disord* 2020;38:101497.

III. **Mahamud Z**, Håkansson S, Burman J, Zelano J. Retention of antiseizure medications for epilepsy in multiple sclerosis: A retrospective observational study. *Epilepsy Behav* 2021;121:108034.

IV. **Mahamud Z**, Burman J, Zelano J. Temporal trends of epilepsy in multiple sclerosis. *Acta neurologica Scandinavica* 2022.

CONTENT

ABBREVIATIONS

ASM	Antiseizure Medication
CDR	The Cause of Death Register
DMT	Disease Modifying Treatment
EDSS	Expanded Disability Status Scale
ICD	International Classification of Diseases
MS	Multiple Sclerosis
NPDR	The National Prescribed Drug Register
NPR	The National Patient Register
PPMS	Primary Progressive Multiple Sclerosis
ROMS	Relapsing-Onset Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SMSreg	The Swedish Multiple Sclerosis Register
SPMS	Secondary Progressive Multiple Sclerosis

INTRODUCTION

This thesis explores the marginally researched field of epilepsy in patients with multiple sclerosis (MS). MS and epilepsy are both serious neurological conditions, but they also share a history of extensive research that has seen to substantial improvements in their respective prognoses. The existing literature suggests that epilepsy in MS is associated with poorer prognosis, but by comparison, research on this condition has been negligible. Improved understanding and management of epilepsy in MS is crucial for the overall efforts to improve MS and epilepsy prognoses to come to fruition.

Concomitant MS and epilepsy is rare. As a result, most existing studies have been small and strictly descriptive in nature, offering limited guidance to clinicians and patients alike. The Swedish MS register (SMSreg) encompasses nearly the entire Swedish MS population and contains patient data stretching back to the 1950s. It offers a golden opportunity to access a large cohort of MS patients with epilepsy and to answer questions that have hitherto been difficult to investigate. The SMSreg has frequently been used for MS research but remains largely unexplored in research on epilepsy in MS. We used the SMSreg to design a series of observational studies venturing to provide fresh insights into diagnosis, prognostic impact and treatment of epilepsy in MS. I hope that this research will have a positive impact on the care of MS patients with epilepsy and that it will act as a stimulant for further research.

As for the outline of this thesis, the *Background* section will acquaint the reader with MS and its relationship with epilepsy. In *Aims,* the thesis' research questions and their rationales are presented, and in *Methods* the tools used for their investigation are briefly expounded on. In *Results and Discussion,* the study findings are scrutinised and integrated with current knowledge. This is followed by a discussion on the *Strengths and Limitations* of the research. Finally, the implications of the research findings are discussed as we look ahead in *Conclusions and Future perspectives*.

BACKGROUND

Multiple sclerosis

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system and the second most common cause of disability among young people of working age after trauma.[1] An estimated 2.8 million people live with MS worldwide. The majority live in countries of higher latitudes and approximately two-thirds are women. The average age at diagnosis is 32 years.[2] Sweden has an MS prevalence of about 189/100,000, which is among the highest globally.[3]

The cause of MS is still uncertain, but it is primarily believed to be of autoimmune origin.[4] According to the prevailing theory, lymphocytes in peripheral blood are activated by antigens that resemble myelin, become autoreactive and infiltrate the central nervous system (CNS) where they cause demyelination. Demyelination occurs in bouts and in well demarcated areas preferentially in periventricular white matter, although the entire CNS can be affected. Inflammatory lesions, also known as MS plaques, spaced out in time and location, are pathognomonic for MS and are required for its diagnosis. They can be verified through clinical evidence, history suggestive of a lesion, and/or magnetic resonance imaging (MRI).[5]

The early stage of MS is termed relapsing-remitting MS (RRMS). It is a phase where patients can experience sudden decline in bodily or cognitive functions corresponding to the severity and location of a lesion, followed by gradual complete or incomplete recovery depending on the compensation margin. As the disease progresses, the inflammatory bouts, also known as relapses, become less frequent and neurodegeneration, subtle at first, becomes increasingly apparent. A patient who starts to deteriorate steadily independently of relapses is said to have converted to secondary progressive MS (SPMS). For a minority of patients, approximately 10%,[2] the disease is characterised by progressive neurodegeneration from the onset and is referred to as primary progressive MS (PPMS). MS cannot be cured, but disease modifying treatments (DMTs) can significantly reduce relapse rate,[6] disability progression[7] and delay conversion to SPMS.[8]

MS frequently coexists with other diseases,[9,10] and among neurological comorbidities, epilepsy is second only to migraine in prevalence.[11] Overall, comorbidities delay diagnosis of MS and initiation of treatment,[12] accelerate disability accrual[13] and increase mortality.[14] To combat this, further research on the relationship between MS and specific comorbidities has been

requested.[15] Knowledge on the effects of comorbid epilepsy on MS prognosis, for example, has been deemed insufficient.[16]

Epilepsy

Epilepsy is defined as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition".[17] It is one of the most common neurological diseases globally, affecting approximately 50 million people worldwide,[18] of which children and the elderly make up the majority.[19]

Typically, two unprovoked epileptic seizures are required for the diagnosis of epilepsy and history-taking or observation of the seizures is sufficient for diagnosis.[19] An epileptic seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain".[17] The term *unprovoked* refers to the absence of a potentially triggering condition. Seizures that occur in direct or close temporal association ($\leq$ 7 days) with a systemic or brain specific insult are termed *provoked* or *acute symptomatic* seizures.[20] These seizures typically have a low recurrence risk[21] and are not sufficient for epilepsy diagnosis.[22]

The process of epilepsy development is referred to as epileptogenesis and typically involves changes to cortical signalling.[23] Its aetiologies include structural, genetic, infectious, metabolic, immune and neurodegenerative causes.[24] More than one aetiology can be identified in the same patient.[25] Acquired changes are more common than innate ones,[24] although in approximately half of all epilepsy cases the aetiology is unknown.[19]

Both pharmacological and non-pharmacological options are available for the treatment of epilepsy. Antiseizure medications (ASMs) are the mainstay of treatment. They aim to suppress seizures and do not cure the underlying epilepsy.[26] Nevertheless, about a third of patients experience refractory epilepsy[27] which is defined as "the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[28] Examples of non-pharmacological options include neurostimulation, ketogenic diet and surgery.

Acquired epilepsy in MS

An estimated 3 – 4% of MS patients have epilepsy, which is approximately three times the prevalence in the general population.[29] Seizures can be the presenting symptom of MS,[30-32] but typically appear during the first decade after MS diagnosis.[30,33,34] The seizures have predominately been described as focal motor[31,32,35,36] with frequent secondary generalization.[33,35,37] Approximately 5-36% of MS patients with epilepsy experience status epilepticus.[31,32,38-43] In one study, this translated into a seven times higher prevalence of status epilepticus in MS patients compared to general population controls.[44] Both provoked seizures associated with MS relapses and unprovoked ones have been reported, although unprovoked seizures seem more common.[45]

Epilepsy is most prevalent among patients with considerable disability and progressive forms of MS.[44] Other risk factors include paediatric onset of MS, long disease duration and high load of juxta and intracortical lesions.[41,44,46,47] Unlike epilepsy in general, male sex is not associated with an increased risk of epilepsy in MS.[44,46]

Aetiology and pathogenesis

The cause of epilepsy in MS is uncertain. The relatively low incidence of epilepsy in MS has induced some authors to propose the cooccurrence of the two diseases to be a mere coincidence.[36,45] In fact, 25 – 50% of MS patients with epilepsy are reported to have competing causes of epilepsy such as stroke and traumatic brain injury.[33,48,49] The proportions of competing causes of epilepsy before and after MS onset are however comparable,[49] while the incidence of epilepsy is higher after MS onset as opposed to before,[44,50] suggesting a causal relationship between MS and epilepsy. Therefore, the dominant opinion is that the development of epilepsy in MS is linked to the pathogenesis of MS.

MS lesions affecting the cortex are more common in MS patients with epilepsy,[51,52] and have repeatedly been suggested to be involved in epileptogenesis.[37,53] Fresh cortical lesions are believed to provoke seizures through intense inflammation and oedema which increase neuronal activity and lower the seizure threshold.[54] In later stages, chronic lesions disrupt normal cortical architecture through gliosis[35,55] and sustain abnormal neuronal activity through smouldering inflammation[56] making them epileptogenic foci. Other factors suggested to either exacerbate the above or to independently cause seizures are diffuse cortical inflammation,[51] selective demyelination of inhibitory GABAergic interneurons[57] and

neurodegeneration,[58] which can also be seen in MS patients with epilepsy. In summary, structural, immune and neurodegenerative aetiologies have been proposed.

The cortical lesion hypothesis offers an explanation for the acute symptomatic *vis-á-vis* unprovoked nature of seizures in MS. It is supported by the increased incidence of focal seizures in MS,[31,32,35] correlation between appearance of new cortical lesions and seizure recurrence[59] and correlations between lesion location and patients' ictal symptoms and electroencephalogram (EEG) activity.[60,61] The hypothesis has however been questioned due to the ubiquitousness of cortical lesions and yet relatively low prevalence of epilepsy in MS.[54] According to autopsy studies, cortical lesions can be observed in more than 90% of MS cases.[36] As a retort, the number, volume and location of cortical lesions rather than their mere presence has been proposed to be decisive. High lesion load in the temporal lobe, for example, has been identified to be especially associated with epilepsy.[35,62]

Diagnosis

Diagnosis of epilepsy in MS follows the general diagnostic workup for epilepsy.[25] In 2014, the clinical definition of epilepsy was revised from necessitating two unprovoked seizures to allowing diagnosis after a first seizure if the probability of a second seizure is at least 60% within 10 years.[22] The 60% threshold signifies the lower limit of the 95% CI of the estimated risk of a third seizure at four years.[22,63] Hence, the new definition would allow for earlier diagnosis and treatment of epilepsy in patients with high recurrence risk, such as in stroke.[21] Although tempting to start ASM after a first seizure in all patients with severe aetiologies, severe underlying disease does not necessarily imply increased recurrence risk above the diagnostic threshold. For example, the risk of a second seizure following traumatic brain injury is 46.6% (95% Cl 30.4 – 66.3).[21] At the time of the introduction of the new definition, the risk of a second seizure was unknown for most neurological diseases associated with seizures, including MS.

Impact of epilepsy on MS

Complications of epileptic seizures are many, including increased risk of depression, trauma and sudden death.[64,65] Comorbid epilepsy may thus mediate worse prognosis, but studies exploring its associations with MS prognosis are few. Of what is known, epilepsy in MS is associated with more severe MS symptoms[47] and increased rates of relapses,[41] disability accrual[35,44] and cognitive decline,[66] as well as lower employment rates[47] compared to MS patients without epilepsy. The effect of epilepsy on definitive endpoints such as conversion to SPMS and death is however uncertain. For instance, both

unchanged[14] and increased mortality[48] in association with epilepsy have been reported.

Treatment

Antiseizure medication

The treatment of choice for preventing seizures in MS is ASM. Reportedly, all available ASMs have been used for seizures in MS, but the optimal treatment still remains uncertain.[16] No clinical trials investigating ASM treatment in MS exist[67] and so observational studies have been crucial for our knowledge of ASM treatment response and tolerability.[37] Existing studies describe that most patients, approximately 50 – 80%, receive monotherapy,[30-34] that older ASMs are preferentially prescribed,[33,68] that one-year seizure freedom ranges between approximately 20 – 80%[33,40,60,69,70] and that MS patients have an increased susceptibility to the adverse effects of ASMs.[33,68] Alongside classic adverse effects, MS patients can experience adverse effects mimicking MS relapses, objectively showing increase in Expanded Disability Status Score (EDSS). In one study, relapse-like adverse effects were reported in a third of patients prescribed carbamazepine at relatively low dosages.[68]

Studies evaluating ASM for epilepsy in MS have only provided descriptive information and do not comment on treatment response to specific ASMs.[37] Thus, evidence available for clinicians initiating ASM in MS patients with epilepsy is limited.

Disease modifying treatment

The possibility of treating epileptic seizures with DMTs has also been discussed.[71,72] DMT has been recommended for evident acute symptomatic seizures associated with relapses.[73] However, a positive effect on unprovoked seizures has been suggested as well. Some case studies, for example, report of MS patients with severe refractory epilepsy and frequent status epilepticus whose seizures reduced dramatically after starting treatment with natalizumab.[74,75]

DMT has been demonstrated to reduce the accumulation of cortical lesions, progress of cortical atrophy, disability progression, relapse rate, cognitive impairment and delay progression to SPMS.[7,76-78] These positive effects are even more pronounced with newer DMTs. Further, DMT may be somewhat effective against neurodegeneration.[79,80] Thus, DMT has a positive impact on some of the risk factors and correlates of epilepsy, but its effect on epilepsy occurrence is yet to be investigated. Moreover, it has been proposed that the relatively low prevalence of epilepsy in MS *vis-à-vis* the ubiquitous cortical

damage could be due to the high prevalence of DMT and its potentially protective effects,[55] but this is also unconfirmed.

AIM

In essence, this thesis aimed to shed light on the impact of acquired epilepsy on MS as well as its diagnosis and treatment. An overview of the specific aims of the included papers and their rationales are as follows:

TABLE 1 Aims and rationales of included papers

Paper	Aim	Rationale
I Risk of epilepsy after a single seizure in MS	To estimate the risk of epilepsy diagnosis after a first unprovoked seizure in MS	Epilepsy can be diagnosed after a single seizure if the risk of a second seizure is at least 60%. The risk of a second seizure in MS was unknown
II Prognostic impact of epilepsy in MS	To estimate risk of conversion to SPMS following epilepsy diagnosis. To estimate and describe epilepsy-associated mortality in MS	The effect of epilepsy on risk of conversion to SPMS and mortality is uncertain
III Retention of ASMs for epilepsy in MS	To describe ASM prescription patterns. To compare retention rates of initial ASMs	ASMs for epilepsy in MS have only been described in small materials. Retention rates of ASMs for epilepsy in MS were unknown
IV Temporal trends of epilepsy in MS	To estimate prevalence and incidence of epilepsy in MS over the past three decades	The effect of the introduction of DMT on epilepsy frequency in MS is unknown

METHODS

Study design

The studies in this thesis are all observational and register-based. Three are cohort studies including MS patients solely while one also includes controls from the general population. The register-based study design was chosen due to its suitability for including large numbers of cases with rare exposures (MS) and the possibility of detecting rare outcomes with conceivably long latency (epilepsy). The observational study, drawing data from prospectively kept records, is the most common study design in studies on epilepsy in MS. Previous studies have included hospital[40,50,70] or population-based[34,44] MS cohorts and extracted data from general medical registers.[14,48] We used an MS specific register, the Swedish MS register (SMSreg), to identify a nationwide study cohort and supplemented it with a series of national registers.

Study population

From the SMSreg, approximately 80% of prevalent MS cases in Sweden, as well as some deceased cases, were available for our studies.[81] Depending on the research question, different inclusion and exclusion criteria were applied to define the study population as shown in the table below:

TABLE 2 Selection of study populations for the studies included in the thesis

Paper	**I** Risk of epilepsy after a single seizure in MS	**II** Prognostic impact of epilepsy in MS	**III** Retention of ASMs for epilepsy in MS	**IV** Temporal trends of epilepsy in MS
Inclusion criteria	MS onset between 1991 – 2014 First seizure code after MS onset	MS onset between 1991 – 2014	MS onset between 2005 – 2014 First seizure code after MS onset First ASM after first code for seizure ASM monotherapy at first prescription	MS onset between 1991 – 2018
Exclusion criteria	Epilepsy code before first seizure code Competing cause of first seizure	Epilepsy code before MS onset		
Final cohort size	289 (Controls 222)	10,383	129	14,557

Registers and variables

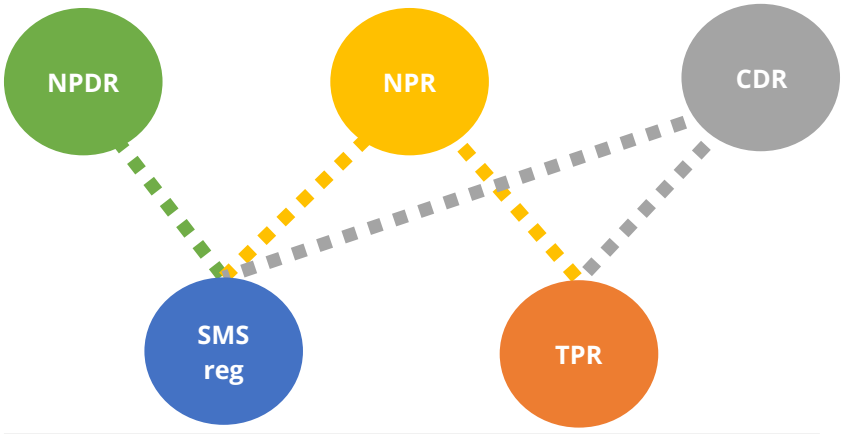
Numerous nationwide registers are available for research in Sweden. Governmental agencies such as The National Board of Health and Welfare and Statistics Sweden manage basic registers such as The Cause of Death Register. Reporting to these registers is compulsory. Disease-specific registers on the other hand are usually run by organisations of healthcare professionals and are termed National Quality Registers when endorsed by the government. In this thesis, several registers managed by governmental agencies and one National Quality Register, i.e., the SMSreg, were used.

After requesting data from register holders, linkage and de-identification was done by Statistics Sweden before the data was delivered to us. All residents

staying at least one year in Sweden are assigned a unique personal identity number by which they are identified in the various registers, and by which linkage is facilitated.

Below follows a description of the registers used and the related variables extracted.

FIGURE 1 Registers used and how they were cross-referenced



CDR, The Cause of Death Register; NPDR, The National Prescribed Drug Register; NPR, The National Patient Register; TPR, The Total Population Register

The Total Population Register (TPR)

This register contains basic demographic information on the population of Sweden such as date of birth, sex and civil status. It is routinely used to produce statistics for political decision making and to supply general population controls for research.[82]

The general population controls used in study I were taken from the TPR.

The National Patient Register (NPR)

The NPR records contacts with healthcare providers expressed as diagnostic codes according to the International Classification of Diseases (ICD). It covers both public and private caregivers and contains all in-patient

diagnoses since 1987, as well as diagnoses for specialist outpatient visits since 2001. Reporting out-patient visits became mandatory in 2005.

We used the NPR to identify epilepsy-related diagnoses in cases as well as controls. Additionally for study I, we extracted all codes registered at the first seizure to exclude study persons with competing causes of seizure. The NPR has been validated for epilepsy diagnoses where it demonstrated 90% accuracy in unselected deceased patients[83] and 94% accuracy in MS patients.[33]

To avoid inclusion of pre-existing epilepsy as incident cases at register start (1987), we allowed five years to elapse before study start (1991) for three of our studies.[84]

The Cause of Death Register (CDR)

The CDR was established in 1961 and contains data from medical death certificates. It contains variables such as date of death and underlying and contributing causes (ICD codes) of death. Validation studies have revealed 77% overall accuracy of causes of death in the CDR. Missing data is rare, and only 0.9% of all deaths were missing an underlying cause in 2015.[85]

We used the CDR to extract causes of death for study II.

The National Prescribed Drug Register (NPDR)

The NPDR contains data on all dispensations of prescription drugs made at Swedish pharmacies since 1st July 2005. Drugs are registered according to Anatomical Therapeutic Chemical (ATC) codes together with patients' personal identity numbers. Reporting to the NPDR is mandatory and automated, and missing data has been found to be negligible.[86]

We used the NPDR to extract dates of prescription and dispensation of antiepileptics (ATC code N03) for study III.

The Swedish MS Register (SMSreg)

The SMSreg was formally established in 2001, but data collection under less formal circumstances has been ongoing since the 1950s. The SMSreg is available to clinicians and can provide an overview of a patient's disease activity and treatment response.[87] The study cohorts in all our studies were

retrieved from the SMSreg. At the first data extraction in 2015, the SMSreg included 15,810 MS patients, of which living cases corresponded to 82% of prevalent cases in Sweden.[81] At the second data extraction in 2018, the number of included MS patients had risen to 20,642, of which living cases corresponded to 86% of prevalent cases.[88] The validity of MS diagnoses in the SMSreg has been reported to be 100%,[89,90] and likewise the validity of remaining variables is reportedly very high.[91] The SMSreg contains MS specific clinical data such as onset and diagnosis dates, disease course and EDSS which were used in our studies.

Ethics

Ethical approval for the included studies was obtained from the regional ethics committee of Gothenburg (approval no. 186–15). Upon enrolment into the SMSreg, patients consent to their collected data being used for research.[87] All data was handled with confidentiality throughout the research process.

RESULTS AND DISCUSSION

Risk of epilepsy after a single seizure in MS (Paper I)

KEY POINTS

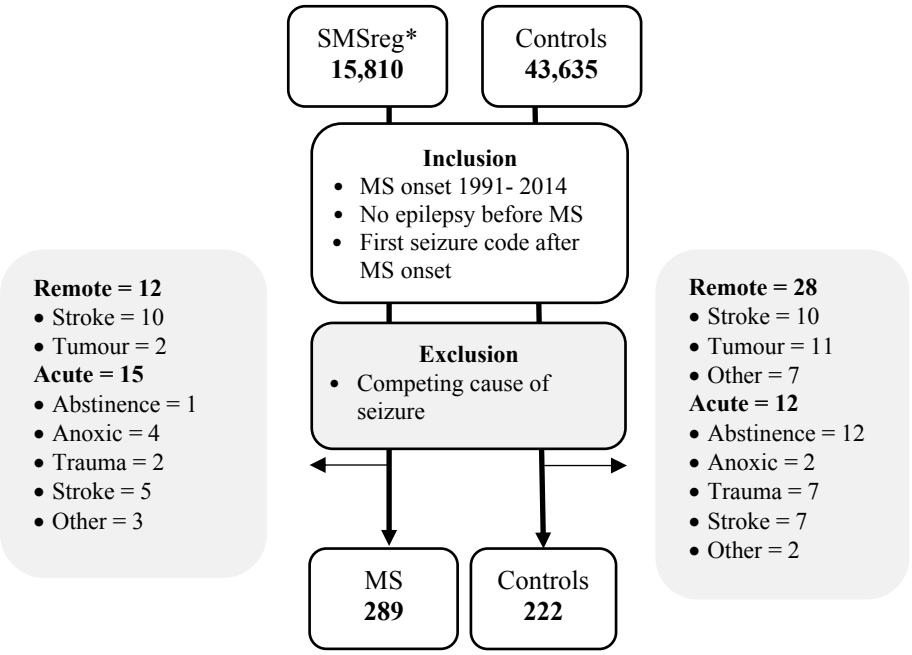
Question What is the risk of an epilepsy diagnosis after a first unprovoked seizure in MS patients?

Findings The risk of epilepsy diagnosis in the unstratified MS cohort was 51.4% (95% CI 44 – 58.9%) and did not differ significantly from controls. The risk tended to be highest in SPMS, 60.7% (95% CI 46.6 – 74.8%).

Implications The risk of epilepsy in MS does not significantly exceed the threshold for diagnosis already after a single seizure (≥60%).

In a first-ever evaluation of seizure recurrence risk in MS, we estimated the 10-year risk of an epilepsy diagnosis in MS patients with a first unprovoked seizure. To increase reliability, age and sex matched controls from the general population, in the ratio 1:3, were employed. Patients with seizures before MS onset or a competing cause of the first seizure were excluded to increase the likelihood of MS related genesis. In total, 289 MS cases and 222 controls were included (**Figure 2**). We used Kaplan-Meier survival analysis with epilepsy diagnosis as event, and death or end of study, whichever came first, as points of censoring.

FIGURE 2 Flowchart of inclusion



*SMSreg, The Swedish MS register

We found the risk of epilepsy diagnosis to be 41.3% (95% CI 33.5 – 49.1) in the controls (**Table 3**), which is consistent with the generally recognised recurrence risk.[92,93] The risk of epilepsy diagnosis in the unstratified MS cohort did not differ significantly from that of the controls, 51.4% (95% CI 44 – 58.9%). Even after stratifying according to MS course, the lower limit of the confidence interval did not exceed the 60% diagnostic threshold for any MS course. Recurrence risk was nevertheless highest in SPMS, 60.7% (95% CI 46.6 – 74.8%), which has been alluded to previously.[66] The results remained unchanged after using more permissive inclusion criteria such as a first seizure within six months of MS onset, or a more permissive definition of epilepsy, i.e., a second code for seizure or status epilepticus more than three months after the first seizure.

TABLE 3 Ten-year risk of epilepsy diagnosis after a first diagnosis of seizure given as percentage with 95% CI

	Controls	MS			
		All MS cases	RRMS	SPMS	PPMS
Seizure or SE	41.3 (33.5 – 49.1)	51.4 (44.0 – 58.9)	46.1 (35.3 – 56.9)	60.7 (46.6 – 74.8)	28.8 (7.24 – 50.4)
Seizure only	41.2 (33.2 – 49.2)	49.1 (35.3 – 56.7)	45.6 (34.6 – 56.6)	57.1 (42.0 – 72.2)	24.6 (3.43 – 45.8)

SE, status epilepticus; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; PPMS, primary progressive MS.

Status epilepticus as a first seizure increases the risk of a subsequent unprovoked seizure at least threefold.[94] Several studies have reported an increased incidence of status epilepticus in MS compared to the general population.[31,32,44] We also found status epilepticus to be more common in MS, both as the first seizure (MS 6.2% vs controls 3.2%) and overall (MS 13.8% vs controls 4.1%). Excluding cases with status epilepticus as the first seizure did not significantly alter the risks of a second seizure (**Table 3**). In analysing MS patients who presented with status epilepticus as their first seizure (n=18), the recurrence risk was 85.9% (95% CI 67.9 – 100%), which exceeded the threshold. Nevertheless, due to the small number of patients, this should be interpreted with caution.

Our findings did not show that MS patients as a group have an excessively increased risk of seizure recurrence legitimising routine early diagnosis and treatment. However, in patients with SPMS, the confidence interval included 60%, hence we cannot confidently rule out that some patients may have a recurrence risk that allows for early diagnosis. We thus propose individualised assessment of patients with suspected elevated risk. In reaction to our findings, Calabrese suggested using grey matter atrophy visualised on non-conventional quantitative MRI as a biomarker for high recurrence risk.[95] Additionally, hippocampal lesion volume has also been proposed as a good predictor of epilepsy in MS patients, area under the curve (AUC) 0.8 (95% CI 0.67–0.91).[62]

The risk of epilepsy tended to be lower in RRMS compared to SPMS. This could be due to less extensive cortical pathology[96] as well as higher likelihood of acute symptomatic seizures associated with relapses. The risk of seizure recurrence is generally up to 80% less after a first acute symptomatic seizure compared to a first unprovoked seizure.[21] However, one study found

seizure recurrence in RRMS to be higher if the first seizure was relapse-associated (55% recurrence) compared to if it was unprovoked (10% recurrence),[40] probably reflecting patients with high versus low disease activity. Thus, the risk of recurrence of strictly unprovoked seizures in RRMS may even be lower than our estimate as we did not exclude potentially relapse-associated seizures. Nevertheless, the risk of epilepsy in RRMS being similar to that of the controls may imply frequent causation by aetiologies other than MS. This highlights the importance of offering patients with RRMS who present with seizures thorough investigation and not arbitrarily ascribing their seizures to MS.

We observed in paper III that two thirds of MS patients with epilepsy received their first prescription of ASM after the first code for seizure and before a code for epilepsy. Although this could be an administrative artifact, screening of medical records of MS patients with epilepsy followed at a tertiary neurology centre in Germany confirmed the same for about a third of their patients.[40] Indeed, the high incidence of status epilepticus and high prevalence of active epilepsy in MS has previously prompted some authors to recommend early initiation of ASM treatment.[36,43] We did not have data on ASM usage for the present cohort. Nevertheless, the impact of potential early ASM initiation on our results is likely small as ASMs reduce the risk of seizure recurrence in short term, i.e., $\leq$2 years,[93] while we assessed 10-year recurrence risk.

In summary, a first seizure in MS does not warrant routine diagnosis of epilepsy. Some subgroups of patients may however be exemptions to this rule, and so further studies are needed to identify risk factors for seizure recurrence to enable clinicians to make individualised assessments.

Prognostic impact of epilepsy in MS (Paper II)

KEY POINTS

Question Does a diagnosis of epilepsy affect the risk of conversion to SPMS and mortality in MS?

Findings Epilepsy diagnosis was not associated with conversion to SPMS, but it increased mortality fourfold in unstratified MS patients. Mortality after epilepsy diagnosis tended to be highest in SPMS, hazard ratio 7.74.

Implications Epilepsy is a negative prognostic marker in MS

Considering the scarce and contradicting information on the effects of epilepsy on MS prognosis,[14,16,48] we investigated the association between epilepsy diagnosis and conversion to SPMS as well as all-cause mortality in a cohort of 10,383 MS patients followed between 1991 – 2014. Additionally, we determined the frequency of epilepsy-related causes of death in MS patients with epilepsy.

The question whether epilepsy diagnosis is a risk factor for SPMS has previously been raised[16] and suggested in a smaller retrospective study from Norway where conversion to SPMS was significantly greater in patients with epilepsy (70%) compared to those without (35%).[32] However, longer disease duration in the patients with epilepsy was mentioned as a possible confounder. To investigate the association between epilepsy and conversion to SPMS, we constructed a Cox proportional hazards model with epilepsy diagnosis as a time-updated variable, SPMS as event and death or study end, whichever came first, as points of censoring. A total of 8,462 patients with relapsing-onset MS (ROMS) were included in the analysis. Our results did not reveal any significant association between epilepsy and conversion to SPMS, hazard ratio (HR) 0.76 (95% CI 0.41 – 1.42); not even after adjusting for age and sex, HR 0.83 (95% CI 0.45 – 1.56). Notably, prevalence of epilepsy was highest among patients with SPMS in our cohort, which might indicate that SPMS is a risk factor for epilepsy rather than the other way around.[44]

Three hundred and twenty-six (3.1%) MS patients died during the study period. Using a similar Cox model but with death as event and study end as a point of censoring, we found epilepsy to be associated with a near fourfold

increased hazard of all-cause mortality (**Table 4**). After stratifying patients according to MS course, the mortality increase tended to be higher in ROMS, HR 5.21 (95% CI 3.16 – 8.6), compared to PPMS, HR 2.47 (95% CI 1.08 – 5.67), and especially pronounced in SPMS, HR 7.74 (95% CI 3.71–16.13). Adjusting the hazards for age and sex did not substantially alter the results.

TABLE 4 Risk of death after epilepsy diagnosis given as hazard ratios (HR) with 95% CI

n	All MS cases 10,220	PPMS 775	ROMS 8,761	RRMS[a] 8,462	SPMS[b] 1,211
Crude HR	4.1 (2.7 – 6.23)	2.47 (1.08 –5.67)	5.21 (3.16 – 8.6)	3.3 (1.35 – 8.07)	7.74 (3.71 – 16.13)
Adjusted[c] HR	3.85 (2.53 – 5.85)	2.28 (0.99 –5.26)	5.48 (3.33 –9.04)	3.84 (1.57 – 9.42)	6.66 (3.18 – 13.92)

MS, multiple sclerosis; PPMS, primary progressive MS; ROMS, relapsing-onset MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS

[a] Patients were censored upon SPMS diagnosis.

[b] Includes patients with known year of conversion and epilepsy diagnosis after SPMS diagnosis.

[c] Adjusted for age and sex.

The magnitude of epilepsy-associated mortality found in our study was slightly higher than previous estimates. A Canadian study[14] reported no significant association between epilepsy and mortality in MS while approximately doubled mortality after epilepsy diagnosis was reported in MS cohorts from the UK[48] and the United States.[97] Besides potential differences in data quality and population characteristics, we lacked data on comorbidities while the authors of the cited studies adjusted for multiple comorbidities. The discrepancy between our study and the Canadian study, where no mortality increase was found, could be due to the authors including epilepsy diagnosed both before and after MS while we restricted the analysis to epilepsy diagnosed after MS onset. Patients who develop epilepsy before MS have a greater likelihood of idiopathic epilepsy, one of the most common aetiologies of epilepsy,[24] which is associated with no or borderline increase in mortality.[98] Nevertheless, our results are consistent with previous findings that acquired epilepsies in general are associated with increased mortality.[99]

MS was the most common underlying cause of death in MS patients with epilepsy (42.9%). Overall, the causes of death in MS patients with epilepsy did not differ significantly from those without epilepsy in our cohort (**Figure 3**), nor from other MS cohorts.[100,101] Epilepsy was an underlying or contributing cause of death in approximately 18% of MS patients with epilepsy (**Table 5**). In general, epilepsy-related causes of death tend to be

more common than unrelated causes in people with epilepsy.[102] However, for individuals with acquired structural aetiologies, where mortality is also greatest, the underlying disease rather than direct seizure-related causes are believed to explain the excess mortality.[99,102] Our results indicate that this might be valid for MS as well, as mortality was greatly increased but epilepsy-related death was relatively infrequent. This is further supported by highest mortality being recorded for SPMS where disease severity is also the greatest.

FIGURE 3 Underlying causes of death in MS patients with and without epilepsy

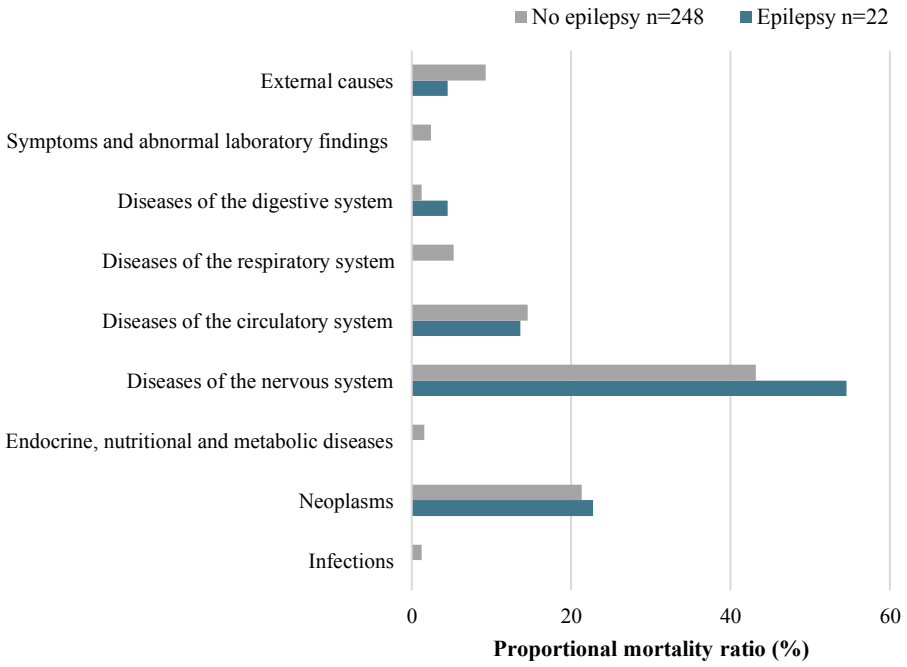


TABLE 5 Death from epilepsy-related diagnoses in the 22 deceased cases with MS and epilepsy

	n	PMR% (95% CI)
Underlying COD		
Epilepsy	1	4.55 (0.12 – 22.84)
Status epilepticus or seizure	0	0
Contributing COD		
Epilepsy	3	13.63 (2.91 – 34.91)
Status epilepticus or seizure	0	0
Epilepsy as underlying or contributing COD	4	18.18 (6.71 – 39.12)

COD, cause of death; PMR, proportional mortality ratio

Among directly seizure-related causes of death in MS, death after acute symptomatic seizures[103] and status epilepticus[31] as well as one case of sudden unexpected death in epilepsy (SUDEP) (O. Sveinsson, personal communication, 22nd November, 2018)[83] have been described. We did not detect any status epilepticus. Additionally, we were unable to study SUDEP as its ICD-code was introduced in 2018,[104] which was after the conclusion of our study. Notwithstanding, epilepsy-related causes of death are frequently underreported[104] and might have been underestimated in our study too.

Our results indicate that epilepsy is a marker of severe MS, although it does not predict conversion to SPMS. Our findings may thus support the suggestion to integrate epilepsy into EDSS as a symptom of MS aggravation.[55] However, unfavourable effects of epilepsy on MS disease course cannot be ruled out. Epilepsy is associated with disruptions of the blood brain barrier and increased permeability to immune cells, which in MS may increase disease activity.[74,105] In fact, levels of proinflammatory markers in cerebrospinal fluid have been found to be significantly higher in MS patients with epilepsy compared to epilepsy free counterparts more than six months after seizure occurrence.[106] Additionally, epileptogenic foci can inhibit remyelination[57] and induce cell death.[105] Clinically, good seizure control has been linked to better cognitive performance and reduced MS disease activity.[42,107] Thus, attaining good seizure control could be important for the prognosis of both MS and epilepsy.

ASM treatment of epilepsy in MS (Paper III)

KEY POINTS

Question Which are the most common ASMs prescribed as initial monotherapy for epilepsy in MS? How do they compare?

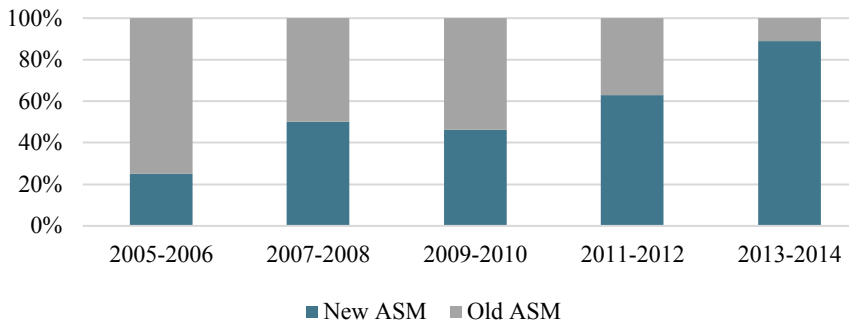
Findings In a cohort of 129 MS patients with epilepsy, the most common ASMs at treatment start were carbamazepine (29.5%), lamotrigine (25.6%) and levetiracetam (14.7%). Lamotrigine tended to have the highest retention rates (1 year: 87.5%, 5 years: 74.4%) followed by carbamazepine (1 year: 60.5%, 5 years: 52.2%) and levetiracetam (1 year: 60.2%, 5 years: N/A). Retention rates for valproate and phenytoin were 50% or lower. Retention on newer and older ASMs, as groups, were comparable.

Implications Newer ASMs should be considered more often as initial monotherapy for epilepsy in MS.

To shed light on optimal ASM treatment for epilepsy in MS, we used the NPDR to extract information on the initial ASMs prescribed after the first code for seizure in MS patients with epilepsy and compared their retention rates. Since the NPDR was started in 2005, we included patients with MS onset after 2005 only, while study end remained 2014. A total of 129 MS patients with epilepsy were included.

The proportion of newer ASMs prescribed as initial monotherapy steadily increased during the study period (**Figure 4**). Considering the entire study period however, the proportion of newer (51%) and older (49%) ASMs did not differ significantly ($p = 0.914$). Patients who were prescribed old versus new ASMs did not differ significantly in the baseline characteristics age, sex or MS course at treatment start.

FIGURE 4 Proportions of new and old ASMs prescribed at treatment start during the study period



ASM, antiseizure medication

Similar to earlier reports,[33,68] we found carbamazepine (29.5%) to be the most prescribed ASM at treatment start (**Table 6**). This could be a cultural preference as carbamazepine was the most commonly prescribed ASM in Sweden at the time of the study as well.[108] However, there are reasons for preferring carbamazepine particularly for MS patients, such as its favourable effects on pain and paroxysmal symptoms which affect at least 50% of MS patients.[109] Following carbamazepine, lamotrigine (25.6%) and levetiracetam (14.7%) were the most common initial ASMs, probably reflecting the growing popularity of newer ASMs in general.[110] Nevertheless, their positive effects on paroxysmal symptoms in MS are also being recognised.[111]

TABLE 6 Frequencies of ASM choice at first prescription, subsequent add-on and change

First ASM	*n* (%) (*n*=129)	Mean follow up (years)	Monotherapy throughout (%)	Received add-on (%)	Changed ASM (%)
CBZ	38 (29.5)	3.2 ± 1.5	20 (52.6)	3 (7.9)	15 (39.5)
LTG	33 (25.6)	3.7 ± 2.5	28 (84.8)		5 (3.0)
LEV	19 (14.7)	1.4 ± 1.3	14 (73.7)		5 (26.3)
VPA	13 (10.1)	3.4 ± 3.7	5 (38.5)	1 (7.7)	7 (53.8)
PHT	10 (7.8)	1.5 ± 1.9	4 (40.0)		6 (60)
GAB	8 (6.2)	1.8 ± 2.6	5 (62.5)		3 (37.5)
OXC	3 (2.3)	1.7 ± 0.5	2 (66.7)		1 (33)
CLZ	2 (1.6)	1.7 ± 2.0	2 (100)		0 (0)
PGB	2 (1.6)	1.8 ± 0.1	1 (50)		1 (50)
VGB	1 (0.8)	6.7	0 (0)		1 (100)

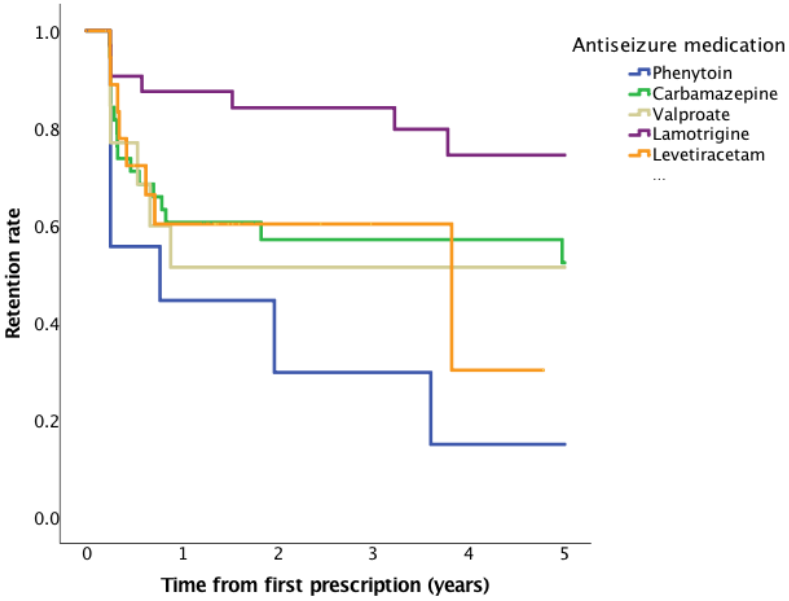
ASM, antiseizure medication; CBZ, carbamazepine; CLZ, clonazepam; GAB, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; VGB, vigabatrin; VPA, valproate.

We next estimated retention rates for ASMs with at least 10 users. Retention rate, or retention of treatment, is a composite measure of the efficacy and tolerability of a drug and is frequently used to compare treatment outcomes for ASMs.[112] Retention rate is typically calculated in the setting of a randomised controlled trial (RCT) but has been estimated in observational studies as well.[113] We defined retention as the continuance of ASM dispensation, and treatment end as the lapse of at least a year without a new dispensation or change of ASM. Treatment end was dated three months after the final dispensation as drugs are typically prescribed for intervals of three months in Sweden. According to the International League Against Epilepsy, a follow-up of at least 48 weeks is sufficient to assess response to an ASM as it allows ample time for treatment adjustment.[112] Using Kaplan-Meier survival analysis, we retrospectively estimated both one and five-year retention rates of the initial ASMs. Patients were followed from the first dispensation of ASM to treatment end (event) and censored upon death or study end (2014), whichever occurred first.

The retention rate of lamotrigine was at one year: 87.5% (95% CI 76 – 98.9), and at five years: 74.4% (95% CI 57.3 – 91.5) (**Figure 5, Table 7**). The retention rate of carbamazepine was at one year: 60.5% (95% CI 45 – 76), and at five years: 52.2% (95% CI 34.9 – 69.4). Discontinuation tended to be lower on lamotrigine compared to carbamazepine, HR 0.41 (95% CI 0.17 – 0.99). Levetiracetam had the third highest retention rate, 60.2% (95% CI 37.2 – 83.2) at one year, but observation time was too short to estimate it at five

years. Its retention did not differ significantly from that of carbamazepine however, HR 1.11 (95% CI 0.47 – 2.62). To compare, Dagiasi *et al.*, described retention of the initial ASMs for 44 MS patients with epilepsy identified from Swedish medical records between 2000 and 2017 and found a 100% retention with levetiracetam while only 52% remained on carbamazepine and 50% on lamotrigine at last follow-up.[33] Follow-up times for the different ASMs were not specified. Not more than half of patients prescribed valproate or phenytoin in our study continued with these after a year. Among the 44 (34.1%) patients who changed ASM, the most common choices were lamotrigine (27.2%) and levetiracetam (22.7%).

FIGURE 5 Survival adjusted retention of the first prescribed ASM



	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**					

ASM, antiseizure medication

TABLE 7 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)	N/A	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)

ASM, antiseizure medication

Information on the reasons for discontinuation was unavailable in the registers we used. According to some previous observations, drug resistance at ASM initiation in MS is low[34] while adverse effects are the most common reasons for ASM discontinuation in MS patients with epilepsy.[33] Discontinuation appears to be lower with newer ASMs compared to older ones.[33] This seems reasonable as adverse effects on newer ASMs are reportedly less frequent in MS[68] and no significant interactions between newer ASMs and MS drugs have been identified, while some older ASMs, such as carbamazepine, are well known enzyme inducers.[73] We were however unable to confirm this. Neither were we able to identify any significant predictors of discontinuation looking at several baseline characteristics (**Table 8**). Nevertheless, the non-inferiority of newer ASMs and their milder side-effect profiles supports their preference as initial monotherapy.

TABLE 8 Crude hazard ratios (HR) of the effect of baseline factors on discontinuation of the first ASM

	HR (95% CI)
Age at MS onset	1 (0.97 – 1.02)
Age at first seizure	1 (0.97 – 1.02)
Age at epilepsy diagnosis	0.99 (0.97 – 1.02)
Male	0.7 (0.37 – 1.29)
New ASM	0.6 (0.34 – 1.04)
PPMS	1.46 (0.62 – 3.44)
RRMS	0.93 (0.51 – 1.68)
SPMS	0.89 (0.5 – 1.56)

ASM, antiseizure medication; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS

In a study following ours, a potential 20 – 27% improvement of individual MS patients' five-year retention rates was identified had all patients in our cohort received the ASM with highest overall retention or highest retention according to their sex stratification.[114] Hence, investigations on retention rates of ASMs should be repeated using different MS cohorts so that patients can be offered ASMs with greatest evidence of high retention. This should be coupled with detailed descriptions of treatment response and reasons for discontinuation to identify ASMs that provide greatest seizure freedom with tolerable adverse effects, which is the goal of ASM treatment.[115]

Temporal trends of epilepsy in MS (Paper IV)

KEY POINTS

Question Has the prevalence and incidence of epilepsy been affected by the introduction of modern MS treatment?

Findings Between 1991 – 2018, prevalence of epilepsy among MS patients increased from 0.34% to 2.54% while the incidence showed no significant trend.

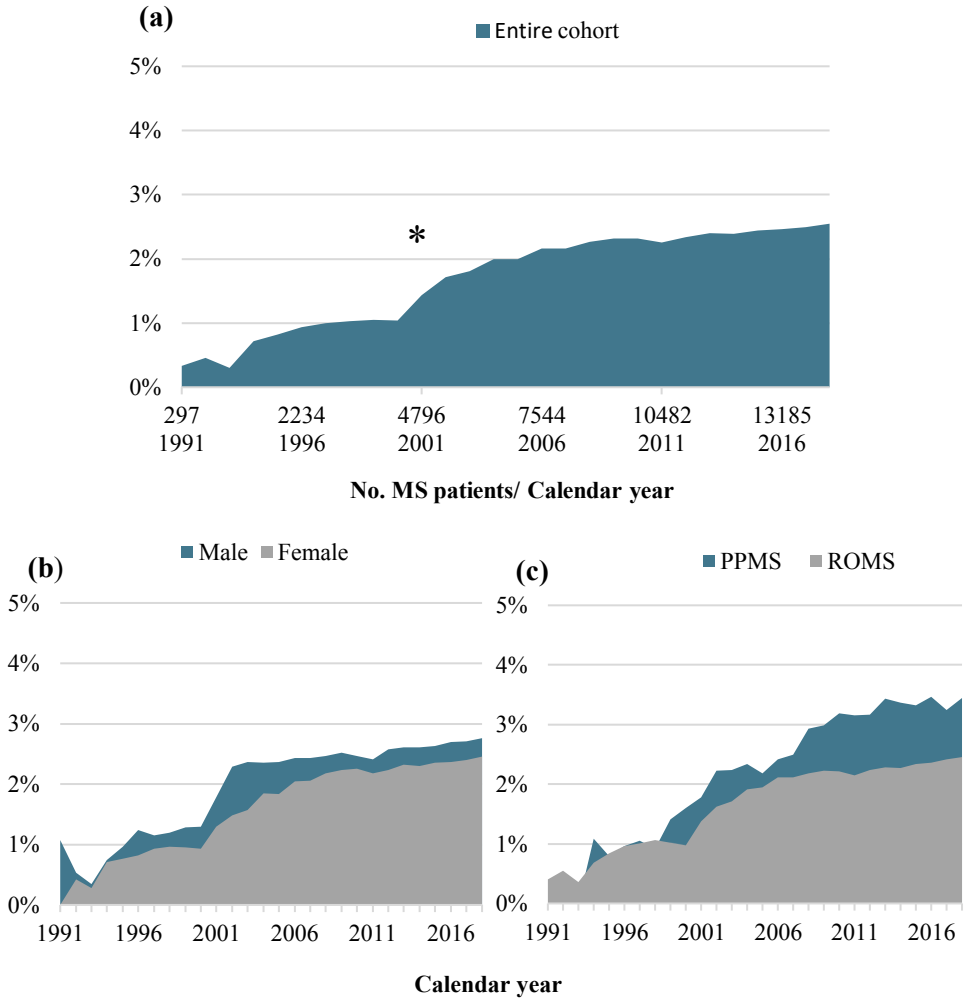
Implication We found no real-world evidence of a protective effect of DMT on epilepsy occurrence in MS.

Considering the favourable effects of DMT on correlates of epilepsy such as grey matter damage,[78] we hypothesised that the incidence of epilepsy in MS should have decreased since the introduction of DMT. To test this, we retrospectively examined changes in prevalence and incidence of epilepsy in a subsection of the Swedish MS population found in the SMSreg during years of introduction and increasing efficacy of DMTs, i.e.,1991 to 2018.

The prevalence of epilepsy in our cohort increased from 0.34% in 1991 to 2.54% in 2018 **(Figure 6a**). This trend was significant with a yearly odds ratio (OR) of 1.26 (95% CI 1.22 – 1.29). In 2001, there was a steep increase in epilepsy prevalence. We attribute this to the addition of outpatient codes to the NPR the same year rather than to any real change in epilepsy incidence as the slope of the curve before and after the increase were comparable (1996–2000: OR 1.23 [95% CI 1.19 – 1.29] and 2003–2007: OR 1.27 [95% CI 1.2 – 1.33]).

We also calculated prevalence according to strata of sex and MS onset form (PPMS vs ROMS) to detect any disproportionate prevalence increase in any subgroup (**Figure 6b, c**). The prevalence changes were however comparable in all subgroups (sex $p = 0.88$; MS onset type $p = 0.918$). Using an interaction term between either sex or MS course with calendar year did not reveal any significant differences either (sex $p = 0.992$; MS onset type $p = 0.797$).

FIGURE 6 Prevalence of epilepsy in MS patients between 1991 – 2018



PPMS, primary progressive MS; ROMS, relapsing-onset MS

We then divided patients into cohorts defined by MS onset years and calculated five and 10-year incidences of epilepsy or any seizure for these temporal cohorts (**Figure 7**). There were no significant differences in the five and 10-year incidences of epilepsy or any seizure between the temporal cohorts, nor did we find any significant trends in the incidence rates (**Table 9**).

FIGURE 7 Incidence of epilepsy or any seizure after MS onset

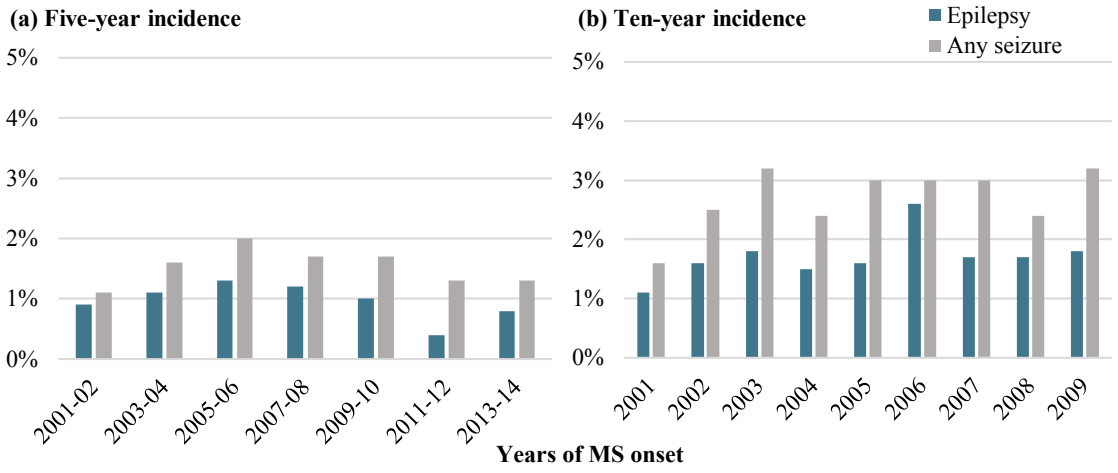


TABLE 9 Incidence range and statistical differences between temporal cohorts

	5-year incidence		10-year incidence	
	Epilepsy	**Any seizure**	**Epilepsy**	**Any seizure**
Range (%)	0.4 – 1.3	1.1 – 2	1.1 – 2.6	1.6 – 3.2
p between cohorts	0.3	0 .626	0.854	0.784
p of trend	0.147	0.951	0.418	0.228

Using Cox regression to adjust the five and 10-year incidence rates of epilepsy for baseline factors did not reveal any significant incidence change in any subgroup during the study period (**Table 10**).

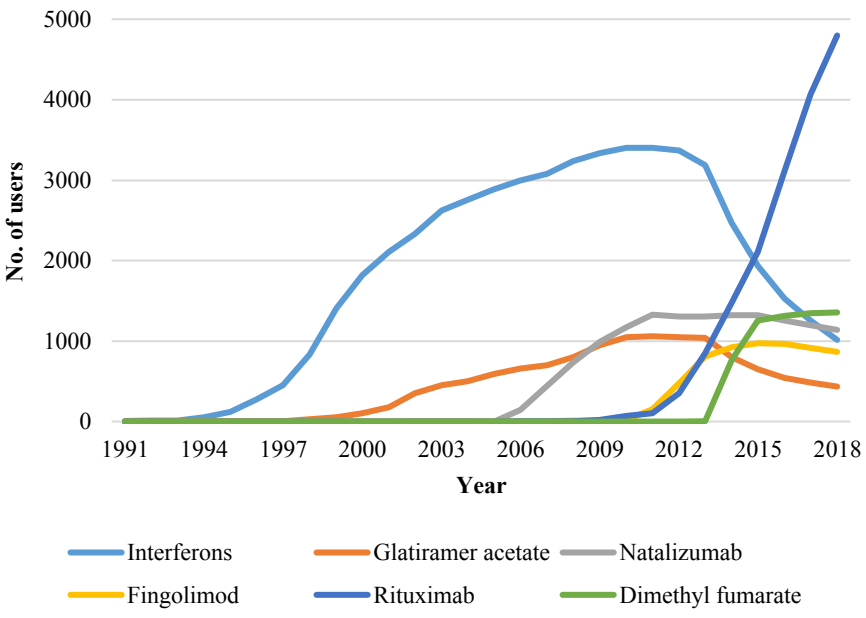
TABLE 10 Yearly change in epilepsy incidence in MS patients between 1991 – 2018 given as HR (95% CI)

	5-year risk[a]	10-year risk[b]
Crude	0.97 (0.91 – 1.02)	1.03 (0.95 – 1.12)
Adjusted for		
Sex	0.97 (0.91 – 1.02)	1.04 (0.95 – 1.12)
Paediatric or adult MS onset	0.97 (0.91 – 1)	1.04 (0.95 – 1.12)
MS onset type	0.98 (0.92 – 1.04)	1.06 (0.96 – 1.15)

[a] Five-year risk estimated for MS onset between 2001 – 2014
[b] Ten-year risks estimated for MS onset between 2001 – 2009

Before discussing the results, it is important to note that we did not determine the treatment status of included patients but assumed an increasing proportion of patients who received DMT, and newer DMTs in particular, as time progressed. DMT has been available in Sweden since the mid 1990s (**Appendix 1, Figure 8**), and since health care is universal and largely tax funded, the Swedish MS population enjoys good access and high reimbursement for DMTs leading to high treatment prevalence.[116] According to treatment statistics from the SMSreg, approximately 80% of RRMS patients aged 40 years or below were receiving active treatment in 2018, while the corresponding percentage in 1998 was roughly 1%.[117] Also, during our study period, the prescription patterns of DMTs recorded by the SMSreg confirmed the successive increased use of newer DMTs (**Figure 8**).

FIGURE 8 Number of users for the most commonly prescribed DMTs 1991 – 2018 according to the Swedish MS register



That epilepsy incidence remained stable during the study period could be interpreted in different ways. Firstly, it could mean that the process(es) behind epilepsy in MS are not modulated by DMT. Cortical lesions and grey matter damage have repeatedly been suggested to be fundamental for the development of epilepsy in MS, but this hypothesis has limitations and cannot be said to fully account for epilepsy in MS.[37,54] We found no difference in epilepsy incidence between ROMS, where cortical lesions are common and DMT usually effective, and PPMS which is marked by essentially treatment refractory neurodegeneration. This further raises questions about the importance of cortical lesions to epileptogenesis.

Secondly, there could have been methodological reasons for not detecting a change in epilepsy incidence over the study period. Perhaps longer individual follow-up would have been necessary to detect the effects of the introduction of DMT, since epilepsy is normally a late complication of MS.[44] In addition, a longer study period could have been necessary to detect the effects of the gradual introduction of newer DMTs. During almost the entire study period, interferons were the most commonly used DMTs (**Figure 8**). Only in 2015 were they superseded by rituximab. In addition, highly effective DMTs were

introduced relatively late, for example natalizumab in 2006 and fingolimod in 2011, not leaving much time to accumulate a critical mass of users. Nevertheless, the effects of interventions cannot satisfactorily be determined with our study design. For example, early initiation of DMT seems important in reversing symptoms of cortical damage,[118] although less than half of MS patients are receiving DMT at the time of their first seizure.[31,40] We did not have data on the prevalence or timing of DMT to assess whether DMT was introduced under optimal conditions to potentially prevent development of epilepsy. Finally, we were unable to detect changes in epilepsy incidence in subgroups defined by sex, age at MS onset or MS onset type. This stratification is however far from exhaustive and further stratification, such as for type of DMT and early versus late treatment start should be investigated.

Prevalence of epilepsy increased steadily during the study period despite unaltered incidence. Lunde *et al*., also report of an increase in epilepsy prevalence from 2.9% to 7.4% between the years 1963 and 2003 in the MS population of a Norwegian county.[34] The authors attributed this to the corresponding increase in MS prevalence observed. No comments were given on epilepsy incidence. Similarly, the prevalence increase found in our study could be due to an accumulation of MS cases, with epilepsy as a complication of long disease duration.

The question whether epilepsy development in MS can be prevented is important and should be investigated further. There has been an ambition in other acquired epilepsies, such as post-stroke epilepsy [119] and epilepsy after traumatic brain injury[120] to prevent the development of epilepsy by intervening during the presumed period of latency. Similar ambitions should apply to MS as well. Additionally, the feasibility of DMT as an option for achieving good seizure control should be studied, as is being done in other epilepsy cohorts.[121]

STRENGTHS AND LIMITATIONS

The observational study design

We used an observational approach to answers questions regarding diagnosis, prognosis and treatment response. Some of these questions are best answered with RCTs, but the scarcity of concomitant MS and epilepsy, compounded by the long latency of epilepsy development, are major impediments and hitherto no RCTs studying outcomes related to MS patients with epilepsy exist. Where RCTs are not feasible, cohort and case-control studies follow in the hierarchy of evidence. Observational studies have an advantage over RCTs of providing real-world results that better reflect clinical reality.[122] This comes at the cost of using non-randomised data and the risk of allocation bias however.

The register-based design

Registers as a source of data allow for the liberty of conducting cohort and case-control studies without their classic disadvantages. For example, in cohort studies, long follow-up without attrition can be achieved.[123] The integration of registers into clinical practice, such as with the SMSreg, is especially advantageous in minimising attrition.[87] As for case-control studies, issues such as recall bias and inability to establish temporal relationships between risk factors and outcomes are minimised.[123]

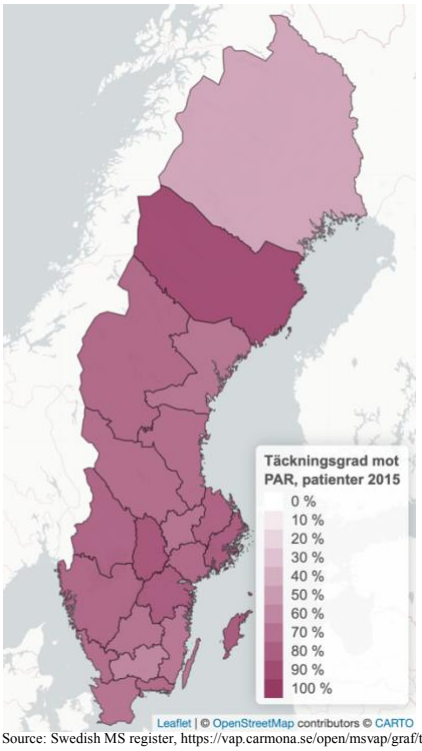
Registers offer a time and cost-effective alternative for accessing large quantities of data over extended periods of time, while requiring minimal or no engagement from study participants.[124] The SMSreg allowed us to follow one of the largest MS cohorts with epilepsy studied so far for up to three decades.

Since the register data used in the studies comprising this thesis were not collected by us, they were not tailored to our research questions. This comes with both advantages and disadvantages. The main advantage is that data collection was not influenced by patient diagnoses or characteristics, thus making any errors, misclassifications or attrition non-differential. Among the disadvantages is the risk of missing data.[123] For example, approximately 10% of MS diagnosis dates were missing from SMSreg in 2021.[90] Another major drawback is that research is limited to the variables chosen by the register holders. This entailed absence of variables that were important for us to reach decisive conclusions, such as the lack of information on the reasons for ASM

discontinuation in paper III. Another implication was the limited availability of relevant confounders. To compensate, we employed sensitivity analyses in some of our studies to determine the robustness of our results with respect to hidden confounders. For example, in estimating epilepsy associated mortality in paper II, we conducted a sensitivity analysis where we excluded patients with brain tumours or stroke as underlying or contributing causes of death as these can cause both epilepsy and death.

We used nation-wide registers; thus, coverage was very high reducing selection bias and enhancing generalisability of our results. The SMSreg for example covered at least 80% of prevalent MS cases in Sweden. Nevertheless, coverage of the SMSreg is not complete which raises questions about the missing proportion of patients and their potential impact on the validity of our results. According to the SMSreg yearly report, inclusion is lowest in northern Sweden[81,88] (**Figure 9**) where long distances and shortage of health care providers are well recognised barriers to healthcare.[125] A Canadian study reported that patients not followed in MS clinics have a higher comorbidity burden, greater disability and lower prevalence of DMT.[126] Hence, there is a small risk that patients with more severe MS, and potentially higher prevalence of epilepsy, have been excluded from our studies. This could have potentially led to an underestimation of epilepsy associated mortality in paper II for example. Another important consideration is that coverage increased for some of the registers during the study period. For example, the expansion of the NPR by addition of outpatient codes gave a corresponding sharp increase in epilepsy prevalence the same year. Fortunately, this was easily distinguishable. The effect of coverage increase of the SMSreg, which was roughly 70% between 1998 and 2018,[127] on our epilepsy prevalence and incidence estimates is harder to determine.

Figure 9 Coverage of the Swedish MS register by county in 2015



Source: Swedish MS register, https://vap.carmona.se/open/msvap/graf/tg_cross/

Validity

An important assumption when drawing conclusions is the validity of exposure and outcome variables. The validity of MS diagnoses in the SMSreg is reportedly absolute,[89] and the validity of remaining variables in the SMSreg is almost as high.[91] Epileptic seizures in MS can easily be mistaken for paroxysmal symptoms, which are much more prevalent, but the validity of epilepsy codes recorded for MS patients in the NPR is approximately 94%.[33]

We did however lack validity data for some of our variables, such as for seizure code in MS. Furthermore, we used algorithms to define ASM use for epilepsy and ASM discontinuation that had not been validated. For example, a patient was assumed to use an ASM for epilepsy if the prescription was preceded by a code for seizure, no matter how long the interval between these. This may have been insufficient in ruling out other common uses of ASMs in MS such as for pain or paroxysmal symptoms.

Despite the limitations of our studies, the study designs chosen carry great strengths that have enabled us to provide well supported answers to questions that have hitherto remained unanswered or where evidence level was low.

CONCLUSIONS AND FUTURE PERSPECTIVES

KEY POINTS

- A single seizure in MS is not sufficient to diagnose epilepsy
- Epilepsy diagnosis in MS is associated with increased mortality, but not SPMS conversion
- Newer ASMs have comparable retention to older ones in treatment of epilepsy in MS, supporting a shift to newer ASMs as initial monotherapy
- Introduction of DMT has not affected the incidence of epilepsy in MS
- Register-based studies are important for advancing knowledge on epilepsy in MS

This thesis has addressed questions of clinical importance to the marginally researched field of epilepsy in MS. Using a register-based approach, we were able to assemble one of the largest MS cohorts with epilepsy studied so far and investigated questions that have hitherto been difficult to answer due to the low prevalence of concomitant MS and epilepsy. We thus demonstrate the feasibility and necessity of the register-based approach to advance knowledge and clinical practice in the field of epilepsy in MS.

Our finding that a first seizure in MS does not warrant routine diagnosis and treatment of epilepsy brings important input to the debate on when to start ASM. Nevertheless, we found a trend of higher recurrence risk in SPMS and a recurrence risk similar to that of the general population in RRMS, which mirrors the dynamic nature of MS and highlights the importance of individual assessment. Closer characterisation of patients with increased recurrence risk may aid in individual assessments as well as increase our knowledge of the risk factors of epilepsy in MS.

We confirm that epilepsy is a negative prognostic marker in MS in our second study. This could prompt clinicians to take measures to improve the prognosis of their MS patients diagnosed with epilepsy, for instance through optimising treatment of MS and comorbidities. We did not consider the impact of active epilepsy treatment in our study, and so it remains to be investigated whether good seizure control can mitigate the negative prognostic impact of epilepsy. Additionally, the impact of epilepsy on other aspects of MS patients' lives and the potential for their betterment should be

investigated, as the definition of epilepsy also extends to its cognitive, psychological and social consequences.

Our study on ASM retention has direct clinical implications as well. It is the first of its kind and provides data on both short and long-term retention which may offer guidance to the clinician initiating ASM for epilepsy in a patient with MS. We have demonstrated non-inferiority of newer ASMs, which supports a shift to newer ASMs with milder side-effect profiles as initial monotherapy. As discussed earlier, we provide real-world data and corroboration by replication in other cohorts is necessary to increase the evidence level for specific ASMs. Observational clinical studies using common data elements could also be an option to obtain higher resolution data on ASM response and to facilitate better comparisons of ASMs. As adverse effects seem to be the most common cause of discontinuation, a better understanding of the adverse effect profiles of specific ASMs and relating them to patients' MS symptoms may help increase retention. Another interesting and important avenue for research could be assessing the effects of ASMs on MS disease activity in addition to seizure freedom and tolerability. Many ASMs have potential anti-inflammatory activity and may aid in reducing MS disease activity as well.

We were unable to find real-world evidence for a protective effect of DMT on epilepsy development in MS. Our study does not rule out the possibility of preventing epilepsy with DMT however, and we have already given reasons for this, such as limited follow-up during the era of the more effective DMTs. Future studies should follow up for longer and compare epilepsy incidence in untreated cohorts versus treated ones, as well as cohorts stratified according to DMT type. DMTs have different modes of action, and a better understanding of epileptogenesis in MS may reveal if they are apt for preventing epilepsy, and if some DMTs are better suited than others.

Many of our findings reveal the need for a better mechanistic understanding of the development, perpetuance and effects of epilepsy in MS, hence a need for preclinical studies. For this, animal models are crucial but at present they are virtually non-existent for epilepsy in MS. Considering the extensive use of animal models in both MS and epilepsy research however, their development should be feasible. Benefits from such research may even have implications outside of MS since epilepsy in MS potentially shares aetiologies with several other epilepsies, i.e., structural, immunological and neurodegenerative epilepsies.

An iterative process of translational research is paramount to achieving confident and clinically applicable results. This thesis has contributed

observational knowledge and we welcome the addition of preclinical and clinical studies. As for the register-based approach, a reasonable next step could be the merging of MS registers to reap the benefits of larger cohort sizes, such as more extensive subgroup analyses and enhanced generalisability. Researchers should also enter into dialogue with register holders to include additional variables that are of relevance to the care of MS patients with epilepsy, but which also foster research.

Ultimately, understanding epilepsy in MS and improving its prognosis should be viewed as inseparable from the overall efforts to improve MS prognosis and personalised medicine in epilepsy care. As such, the findings in this thesis should be viewed as important groundwork for more comprehensive and clinically relevant research.

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APPENDIX

APPENDIX 1 DMT available in Sweden years 1991 – 2018

Drug	Year of market authorisation (product name)
Interferon beta 1b	1995 (Betaferon), 2008 (Extavia)
Interferon beta 1a	1997 (Avonex), 1998 (Rebif)
Glatiramer acetate	2001 (Copaxone)
Natalizumab	2006 (Tysabri)
Fingolimod	2011 (Gilenya)
Alemtuzumab	2013 (Lemtrada)
Tteriflunomide	2013 (Aubagio)
Dimethyl fumarate	2014 (Tecfidera)
Peginterferon beta 1a	2014 (Plegridy)
Mitoxantrone	2016 (Novantrone)
Cladribine	2017 (Mavenclad)
Ocrelizumab	2018 (Ocrevus)
Rituximab	Not authorised for MS (Mabthera)

Source: The Swedish MS Association and European Medicines Agency