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Second antiseizure medication monotherapy in patients with adult-onset epilepsy: A register-based analysis

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ABSTRACT

Objective: Revision of therapy is fundamental in epilepsy care, since only half of patients achieve seizure freedom and tolerate the first antiseizure medication (ASM). We studied the selection and retention of second antiseizure medication monotherapy in adults who discontinued treatment with one of the three most frequently prescribed first ASMs, and the impact of age or brain comorbidities.

Methods: Using Swedish national registers, we conducted a population-based, retrospective cohort study from 2007 to 2019 on patients age ≥ 30 at the epilepsy diagnosis that had switched to a second monotherapy after the three most common initial monotherapies (n = 7369). Retention rates (RR) were estimated via Kaplan-Meier. Discontinuation of the second monotherapy was defined as 12-month prescription gap or initiation of a third ASM. Analyses were stratified by sex, age, and presence of stroke or dementia.

Results: The three most commonly prescribed second ASMs were carbamazepine, levetiracetam, and lamotrigine. The 1-year retention rate was 63–76% in all patients. For groups with stroke or dementia, the maximal 1-year RRs were 77% and 87%, respectively. After five years, retention rates ranged from 12% to 39%. There were no major differences between ASMs, apart from in patients discontinuing carbamazepine, where lamotrigine had a superior retention compared to levetiracetam as second monotherapy.

Significance: The three most often prescribed second ASMs seem to be suitable treatment options according to present guidelines. The second ASMs' retention rates were initially high in all studied patient groups but dropped to approximately the expected proportion of second monotherapy responders over the next five years. This suggests that therapy revision could be expedited.

1. Introduction

Antiseizure medication (ASM) selection is influenced by the type of epilepsy and individual patient characteristics, such as age, sex, and comorbidity [1]. Just about half of the epilepsy population tolerate and experience good effect of their first ASM [2]. Regarding second ASMs, several factors seem to influence effectiveness. Subsequent ASMs with similar mechanisms of action to previously tried ASMs tend to have similar efficacy and side effects [3]. After a trial-and-error process, two thirds of patients can eventually achieve seizure freedom [2].

Given the high proportion of non-responders to the first ASM, good epilepsy care includes revision of therapy. Compared to that of the first ASM, the response to subsequent treatments has been much less studied. In Glasgow between 1982—2012, 45 % of an initial cohort of 1790 patients achieved seizure freedom on their first ASM; two-thirds were started on an alternative ASM and approximately one fifth of these became seizure-free on their alternative regimen [2,4]. In older patients, researchers in Finland have described a more positive prognosis, with 59 % becoming seizure-free on the first and 63 % on the second ASM [5].

We have previously described high retention rates (RR) for first ASMs in Swedish prescription data, suggesting that therapy revision is not done sufficiently often [6]. In the present study, we aimed to describe the selection and retention of second ASMs in adults with focal epilepsy, focusing on older patients and those with brain comorbidities.

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The aim was to investigate which ASMs were most often selected after the first ASM and to describe for how long adults with focal epilepsy remained on their second ASM.

2. Material and methods

2.1. Registers

The studied RR dataset was originally compiled from comprehensive national Swedish registers: the National Patient Register (NPR), the National Prescribed Drug Register (DR), and the Cause of Death Register (CDR). The NPR records information on specialized health care encounters, achieving complete coverage of inpatient care from 1987 onwards. The register expanded in 2001 to include outpatient visits and emergency room encounters. Reporting to the NPR is mandatory for all healthcare providers. The DR, initiated on July 1, 2005, contains information on all dispensed prescription drugs in Sweden, including dispensing dates. All pharmacies participate and reporting is mandatory/automatic. The CDR includes information on all dates of death and causes of death. All registers are linked by personal identification numbers unique to each Swedish inhabitant.

2.2. Statistical analyses

The RR dataset has been previously described [6]; it includes retrospectively collected data from the above registers spanning 2007 to 2019. For the current cohort study, we adopted the same baseline inclusion criteria as the RR set, but narrowed our focus to the subpopulation that initiated second ASM monotherapy following first treatment with either carbamazepine (CBZ), levetiracetam (LEV), or lamotrigine (LTG) – the three most common first ASMs. The RR dataset included individuals with a first diagnosis of epilepsy, defined as the occurrence of the International Classification of Diseases, 10th Revision (ICD-10) code G40 in the NPR, after January 1, 2007. This allowed for tracking of their entire ASM history, since the DR started in 2005. The specific inclusion criteria encompassed a first diagnosis of epilepsy and a first-ever ASM dispensation following the initial seizure (i.e., the first seizure-related diagnostic code [ICD-10: R568, G40, or G41]). The combination of an ICD-10 code for epilepsy and the prescription of an ASM is highly specific for epilepsy in administrative data [7].

All prescriptions of ASMs (defined as Anatomical Therapeutic Chemical code N03) for the included individuals were identified. Swedish prescriptions are valid for 1 year, and each dispensation is usually sufficient for 3 months of use. ASM discontinuation was, therefore, defined as a lapse of more than 12 months without a new dispensation and was set to occur 3 months after the last dispensation. The RR was calculated by Kaplan–Meier (KM) analysis, and confidence intervals (CIs) were calculated using Greenwood's exponential formula. The initiation date for second ASM monotherapy was set at the discontinuation of the first ASM if the two treatments overlapped, or at the first dispensation otherwise. The survival time (duration of second monotherapy) was calculated until either discontinuation of the second ASM (event), dispensation of a third ASM (event), death (censored), or the study's end date (censored as of December 31, 2019).

Our predefined hypothesis was that patient groups with specific patient characteristics (age, sex, comorbidities) would have significantly divergent retention rates. Initially, we had planned to analyze retention rates for patient groups with combinations of patient characteristics (age, sex, and comorbidities), but these analyses were not possible because of too small groups/too wide confidence intervals. Retention rates were compared with pair-wise log-rank tests over the entire time course (lifeline Python package version 0.27.8), and confidence intervals at years 1, 2, and 5. All analyses were performed in Python version 3.10, SPSS version 27 for Mac, or R version 4.3.1.

2.3. Study population

We included 7369 persons with presumed focal epilepsy (onset after 30 years of age), who initially tried but did not continue with one of the three most common initial medications in this patient group: CBZ, LEV, and LTG [6]. We categorized patient subgroups of interest based on the following criteria: sex, male or female; age, with two subgroups, 30–60 and greater than 60 years of age; comorbidity, in the form of stroke or dementia.

2.4. Ethical permission

This study was approved by the Swedish Ethical Review Authority (approval number 2020–04902). All handling of personal data was done in agreement with Swedish data protection laws.

3. Results

3.1. Selection of second ASM

The most frequently prescribed first ASMs were CBZ, LEV and LTG (Fig. 1A), and these were also the most common second ASMs for patients discontinuing their first (Fig. 1B-D). For patients discontinuing CBZ, LEV was the most common second ASM. Patients discontinuing LEV most often received LTG as their second ASM, and those discontinuing LTG most often received LEV.

3.2. Retention of second monotherapy

We next assessed the duration of the second ASM monotherapy (Table 1). The one-year RRs of the three most commonly prescribed second ASMs were 61–74 % for those discontinuing CBZ, 61–76 % for those discontinuing LEV, and 53–67 % for those discontinuing LTG (Table 2).

n patients discontinuing CBZ, LTG had a higher retention rate than LEV as second monotherapy at two and five years, and than valproic acid at all time points (Fig. 2A). LEV had a superior retention compared to valproic acid at one and two years. Over the entire period, the retention rate was significantly higher with LTG than valproic acid ($p < 0.001$) and LEV ($p < 0.001$), whereas the difference between LEV and VPA was not significant (Fig. 2A). In patients discontinuing LTG, LEV and CBZ had a superior retention compared to valproic acid ($p < 0.03$ and $p < 0.05$, respectively, Fig. 2B). In patients discontinuing LEV, LTG had a superior retention compared to CBZ at one year, but not significantly so over the entire time period, and superior retention compared to valproic acid ($p < 0.001$, Fig. 2C). The results were similar for patients aged 60 and above (Fig. 2D-F). In patients > 60 discontinuing CBZ, LTG was superior to valproic acid ($p < 0.001$) and LEV ($p < 0.001$), whereas the higher retention rate of LEV was just not significantly different from that of valproic acid ($p = 0.05$). In patients > 60 discontinuing LTG, LEV had a significantly higher retention rate than VPA ($p = 0.03$). In patients discontinuing LEV, CBZ and LTG had higher retention rates than VPA ($p = 0.02$ and $p < 0.001$, respectively). For all second monotherapies, the RRs dropped substantially over the subsequent five years, to less than 30 % for almost all ASMs.

3.3. Subgroups

Finally, we analyzed patient subgroups based on sex, age, and presence of stroke or dementia (Supplemental table 1). Men and women who discontinued CBZ, LEV or LTG received the same second ASMs, and RRs of the second ASM were similar. Regarding age, the most common choices of second ASM were the same in patients aged 30–60 as > 60. The RRs were slightly higher in the older patient groups, but not significantly so. Patients with stroke or dementia received the same second ASM as younger patients. The pattern of retention rates was

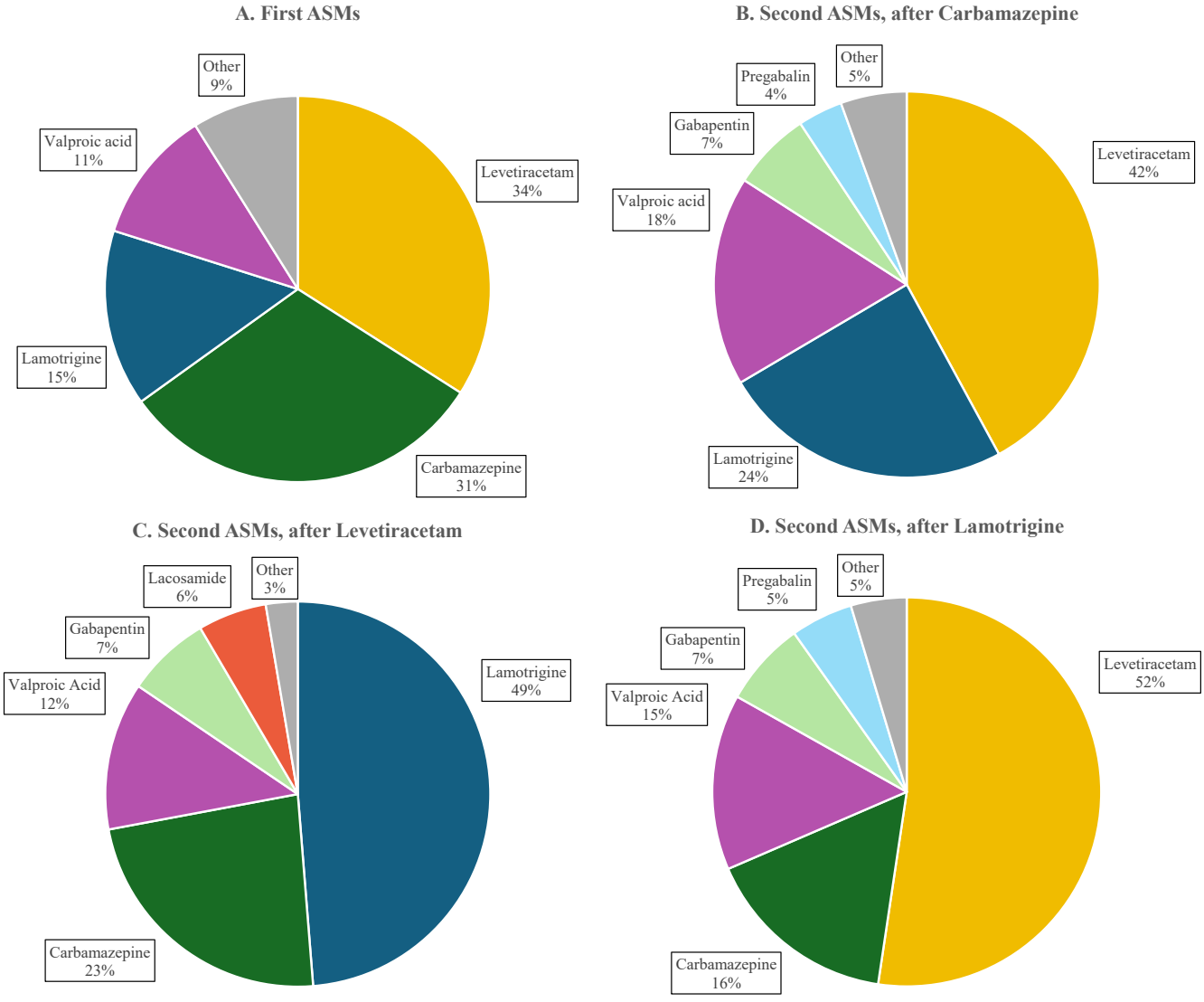

Fig. 1. Prescription frequency of A. first antiseizure medications and second antiseizure medications, after discontinuation of B. Carbamazepine, C. Levetiracetam or D. Lamotrigine.

Table 1
Baseline characteristics of the cohort, stratified by initial ASM.

		First ASM		
	Whole cohort (n = 7369)	**CBZ (n = 3707)**	**LEV (n = 2329)**	**LTG (n = 1333)**
Age at first ASM				
median y (Q1-Q3)	63 (49–74)	62 (49–72)	66 (51–76)	60 (44–74)
30–60 y, n (%)	3119 (42)	1580 (43)	870 (37)	669 (50)
>60 y, n (%)	4250 (58)	2127 (57)	1459 (63)	664 (50)
Sex, n (%)				
Female	3422 (46)	1631 (44)	1052 (45)	739 (55)
Male	3947 (54)	2076 (56)	1277 (55)	594 (45)
Medical history, n (%)				
Stroke	2895 (39)	1529 (41)	953 (41)	413 (31)
Dementia	1566 (21)	827 (22)	465 (20)	274 (21)

similar in all subgroups as in the total population, with the exception of patients with stroke and dementia, where the confidence intervals were sometimes overlapping, perhaps because of small groups.

4. Discussion

In this retrospective cohort study examining second ASM monotherapy for adult-onset epilepsy, we found that CBZ, LEV, and LTG were the most frequently prescribed medications during the study period. The RRs were high initially but declined over 5 years. This pattern in retention rates and the choice of second ASMs were consistent across patient subgroups, regardless of age, sex, or the presence of stroke or dementia.

For all patient groups, the retention of the second ASM was surprisingly high, particularly after one year, given the low likelihood of response to the second ASM [2]. After five years, the RRs of those starting a second ASM had dropped significantly, about 75 %. With sparse seizure intervals, evaluation of the second ASM may take time, but the results still indicate room for improvement and greater vigilance in therapy revision. The most likely explanations for therapy revision after one to five years are problems with tolerability or efficacy [8]. Both reasons for treatment failure could presumably be addressed earlier, with the exception of very rare seizures as discussed above. Importantly, patients starting a second ASM are presumably in contact with an epilepsy care provider that offers therapy revision, so the cohort most likely

Table 2
Retention rates (RRs) and respective confidence intervals (CIs) of second antiseizure medication (ASM) monotherapy.

First ASM	Second ASM	n	1-year RR	95 % CI	2-year RR	95 % CI	5-year RR	95 % CI
Carbamazepine	Levetiracetam	1557	71 %	68–73 %	54 %	51–57 %	28 %	25–30 %
	Lamotrigine	905	74 %	71–77 %	63 %	59–66 %	39 %	35–42 %
	Valproic Acid	650	61 %	57–65 %	45 %	41–49 %	24 %	20–27 %
Levetiracetam	Lamotrigine	1130	76 %	73–78 %	52 %	49–55 %	17 %	15–20 %
	Carbamazepine	541	64 %	60–68 %	46 %	41–50 %	18 %	14–21 %
	Valproic Acid	288	61 %	53–66 %	39 %	32–45 %	12 %	8–17 %
Lamotrigine	Levetiracetam	677	67 %	63–70 %	46 %	42–50 %	19 %	15–22 %
	Carbamazepine	209	63 %	55–69 %	46 %	39–53 %	23 %	16–28 %
	Valproic Acid	189	53 %	44–60 %	36 %	28–42 %	14 %	8–19 %

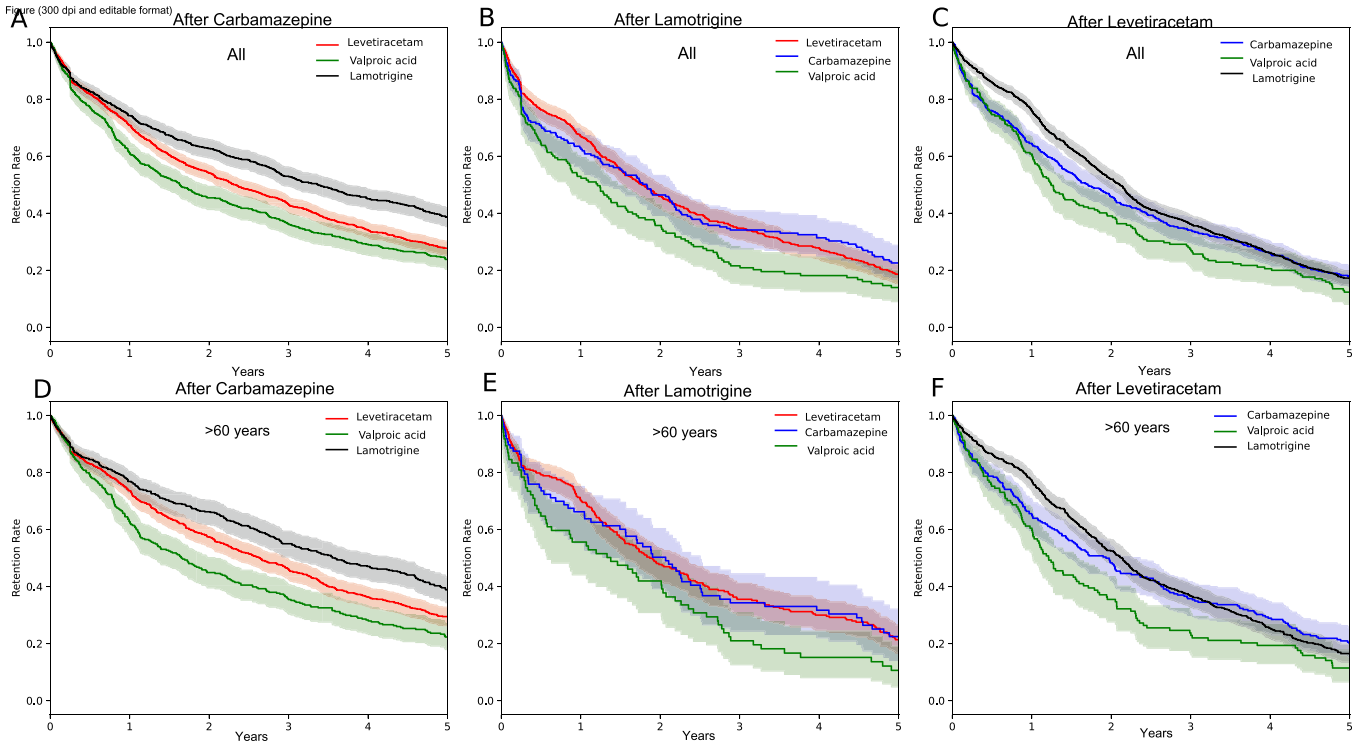

Fig. 2. Retention rates (RRs) of second antiseizure medications in all patients discontinuing A. Carbamazepine, B. Lamotrigine or C. Levetiracetam, and in patients > 60 years of age (D-F).

reflects the better end of Swedish epilepsy care.

Our findings are congruent with the existing literature. The resulting RRs are in agreement with those described in randomized studies on focal epilepsy such as the SANAD study of a heterogeneous population and two previous randomized clinical trials (RCTs) of poststroke epilepsy [8–10]. In Glasgow, approximately one fifth of those starting a second ASM regime responded [4], which is very close to our five-year RRs. A Finnish study found a higher response rate to the second ASM in older patients [5], but the reduction in retention over the subsequent years argues against that being the explanation in our cohort. Other studies on US Medicare data have also identified LEV and LTG as common second ASM [11].

There are a number of limitations to the study. The DR was started as late as 2005, which allows only a few years of ASM tracking, and the algorithm for ASM retention was relatively crude. Since the data is administrative, we do not know the reasons for ASM discontinuation and cannot compare efficacy of second ASMs. LTG had a significantly higher retention rate as a second ASM compared to LEV or VPA in patients discontinuing CBZ. There can be several confounders, like patient characteristics and follow-up, but good efficacy of LTG mimics previous studies like SANAD [8] and SANAD II, in which LTG had better tolerability than LEV [12]. VPA had low retention rates across all subgroups, indicating that since many patients eventually discontinue this drug it may not be an ideal second ASM in the studied patient groups. The reasons for stopping VPA cannot be determined from our database, but presumably relates mainly to tolerability. Other contributing explanations could be that VPA introduced in emergency care as a loading drug in cases of status epilepticus or seizure clusters on a first monotherapy may continue as second monotherapy, but then be revised when the patient sees an epilepsy care provider for concerns regarding tolerability, drug-drug interactions, or that the patient is a woman of childbearing age.

It also seems that many patients during the studied time in Sweden did eventually discontinue their second ASM, which is to be expected from the literature. Since the major reasons for discontinuation is either poor seizure control or side effects, it seems plausible that revision of the second ASM could be expedited. In other article studying second ASMs, treatment failure was usually detected in the first years. However, it is possible that other factors could influence the large drop in retention rate between years 1 and 5. For instance, introduction of non-enzyme inducing ASMs and increased awareness of interactions may have prompted switches from CBZ. Remission could be another factor. There

is also a time lag for register-based studies and the study period form 2007–2019 is a limitation given the many ASMs now available to clinicians. Several new ASMs, such as perampanel, brivaracetam, and lacosamide, have become more popular in recent years. The present study demonstrates feasibility of the method, and new analyses should be performed in a few years for more information on newer ASMs. National registers are updated continuously, which offers an opportunity to incorporate information on new ASMs continuously, but to elucidate their RRs, future studies are needed. Moreover, the 12 year long audit period of this study constitutes a disadvantage, in a way that ASM usage trends have probably changed during this time, with the most characteristic example being the decrease in usage of CBZ and increase in usage of LEV. It is also important to note that the RRs in our study reflect the situation for adult-onset presumed focal epilepsy, and not for other epilepsy syndromes. The strengths of the study include comprehensive access to national registers and inclusion on a nationwide scale, which enhances the external validity of our findings. The combination of a diagnostic code for epilepsy and a prescription for an ASM has been shown to be highly specific for epilepsy[7], and an epilepsy diagnosis in the NPR has a positive predictive value of 90 % for the disease[13].The DR is comprehensive and contains all prescriptions of dispensed drugs in Sweden, making it robust to factors influencing many clinical studies, such as patient relocation.

5. Conclusion

We conclude that patients with adult-onset epilepsy who started second ASM monotherapy were treated similarly across subgroups. The three most commonly prescribed second ASMs align with current Swedish guidelines, yet their retention rates suggest the potential for expedited therapy revision.

CRediT authorship contribution statement

Konstantinos Polychronidis: Writing – original draft, Visualization, Methodology, Investigation. **Samuel Håkansson:** Validation, Software, Resources, Methodology, Investigation. **Saman Hosseini Ashtiani:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **André Idegård:** Writing – review & editing, Visualization, Formal analysis, Data curation. **David Larsson:** Writing – review & editing, Validation, Supervision, Methodology. **Johan Zelano:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J. Z. has received speaker honoraria from Eisai and UCB, and as an employee of Sahlgrenska University Hospital (no personal compensation) he is or has been an investigator in clinical trials sponsored by Bial, UCB, SK life science, GW Pharma, and Angelini Pharma. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.109792.

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