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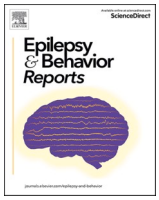

Adherence to anti-seizure medications in the Swedish Prospective Regional Epilepsy Database and Biobank for Individualized Clinical Treatment (PREDICT)

Kerstin Andrén [a,b,*], David Larsson [b,c,d], Fredrik Asztély [a,b], Johan Zelano [b,c,d]

[a] Angered Hospital, SV Hospital Group, Box 63, 424 22 Angered, Gothenburg, Sweden
[b] Institute of Neuroscience and Physiology, Department of Clinical Neuroscience, Sahlgrenska Academy, Gothenburg University, Blå Stråket 7, 413 45 Gothenburg, Sweden
[c] Department of Neurology, Sahlgrenska University Hospital, Blå Stråket 7, 413 45 Gothenburg, Sweden
[d] Wallenberg Center of Molecular and Translational Medicine, Gothenburg University, Box 100, 405 30 Gothenburg, Sweden

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ABSTRACT

The aim of this study was to describe the extent of, and risk factors for, non-adherence to anti-seizure medications (ASMs) in adult people with epilepsy (PWE) in Sweden.

A cross-sectional multi-centre study was performed of PWEs in western Sweden, with data from medical records, and a questionnaire filled in by the participants including self-reports on how often ASM doses had been forgotten during the past year. Participants were categorized into *adherent* if they forgot at 0–1 occasion, and *non-adherent* if they forgot at 2–10 or >10 occasions. Demographic and clinical factors were compared by Chi2- or Fisher's test and a logistic regression model was used to find risk factors for non-adherence.

In the cohort of 416 PWE aged median 43, IQR 29–62 years, 398 patients were prescribed ASM treatment at inclusion, and 39 % (n = 154) were in the non-adherent group. Significant factors in the multivariable analysis were: younger age, seizure freedom the past year, valproate treatment and experiencing side effects.

The rate of self-reported non-adherence was high, illustrating a need for continuous focus on fundamental aspects of epilepsy care. The identified risk factors could enable quality improvement projects and patient education to be directed to those at risk of non-adherence.

1. Introduction

Management of epilepsy requires long-term treatment with anti-seizure medications (ASMs), achieving a successful control of epileptic seizures in up to 70 % of adults [1,2]. Lack of adherence to long-term therapies is a well-known problem in treatment of chronic diseases, contributing to poor health outcomes and increased health care costs [3]. Non-adherence is considered one of the main causes of unsuccessful treatment, and has been associated with an increased risk of seizure relapse, hospitalizations, increased costs, status epilepticus, injuries, and death [3–8].

Sub-optimal adherence is common in people with epilepsy (PWE), but the prevalence varies largely between studies depending on the used methods and definitions of adherence. A review published in 2017 found sub-optimal adherence in 26–79 % of patients in 17 studies [9], and a systematic review published in 2022 on studies using different self-report measures for adherence found rates of sub-optimal adherence between 21 and 95 % in 36 studies, with an estimated average rate of almost 50 % [10]. The most commonly mentioned self-reported reason for non-adherence in the latter review was forgetfulness. Identification of risk factors for low compliance to ASMs could allow for directing measures to improve treatment in those patients. Many studies found associations between non-adherence and younger age, experiencing side effects from ASMs, and recent seizures.

The extent of adherence to ASMs in a routine non-acute clinical care setting in Scandinavia has not previously been described, nor the characteristics of PWEs with low adherence.

The aim of this study was to describe the extent in PWEs of self-reported instances of forgetting to take ASM doses in a regional prospective observational study, and to identify risk factors associated with

* Corresponding author at: Angered Hospital, SV Hospital Group, Box 63, 424 22 Angered, Gothenburg, Sweden.
E-mail addresses: kerstin.andren@vgregion.se (K. Andrén), david.gw.larsson@vgregion.se (D. Larsson), fredrik.asztely@neuro.gu.se (F. Asztély), johan.zelano@neuro.gu.se (J. Zelano).

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these lapses in medication adherence.

2. Materials and methods

2.1. Study design and setting

The study has a multi-center cross-sectional design. Data were collected in the Prospective Regional Epilepsy Database and Biobank for Individualized Clinical Treatment (PREDICT) project (clinicaltrials.org identifier: NCT04559919). PREDICT is a multi-center prospective cohort study on adult patients aged ≥18 years, with an unprovoked seizure or with epilepsy, residing in Västra Götaland County (VGR) in Sweden. The VGR region has a total population of approximately 1.7 million inhabitants, served by six public neurological clinics: five of those participated, while the sixth community hospital with a catchment population of about 260 000 inhabitants, chose not to participate. Patients were included by physicians at routine clinical visits. The catchment area and the number of included patients per center is shown in Fig. 1.

2.2. Study participants

The study start date was on the 15th of December 2020, and data for all so far included PWE fulfilling the diagnostic criteria according to the current International League Against Epilepsy definition (epilepsy with seizure in the last ten or antiepileptic drug treatment in the last five years) [11] were extracted on the 16th of January 2023 for inclusion in the present study. All patients were aged 18 years or above and all received written study information, available in Swedish, English and Arabic, and gave written consent to be included in the study. Exclusion criteria were inability to understand the study information and give own consent, or a life expectancy of less than 2 years.

2.3. Data retrieval

All participants filled out a questionnaire at the time of inclusion. The questionnaire was formulated to capture information on the patients' situation and the influence of epilepsy in their lives. It includes questions about their current occupation, seizure frequency and consequences of seizures, treatment adherence, and side effects (Supplementary file, S1). Data on if, and how often, they had forgotten to take their ASM during the past year were retrieved from the questionnaires:

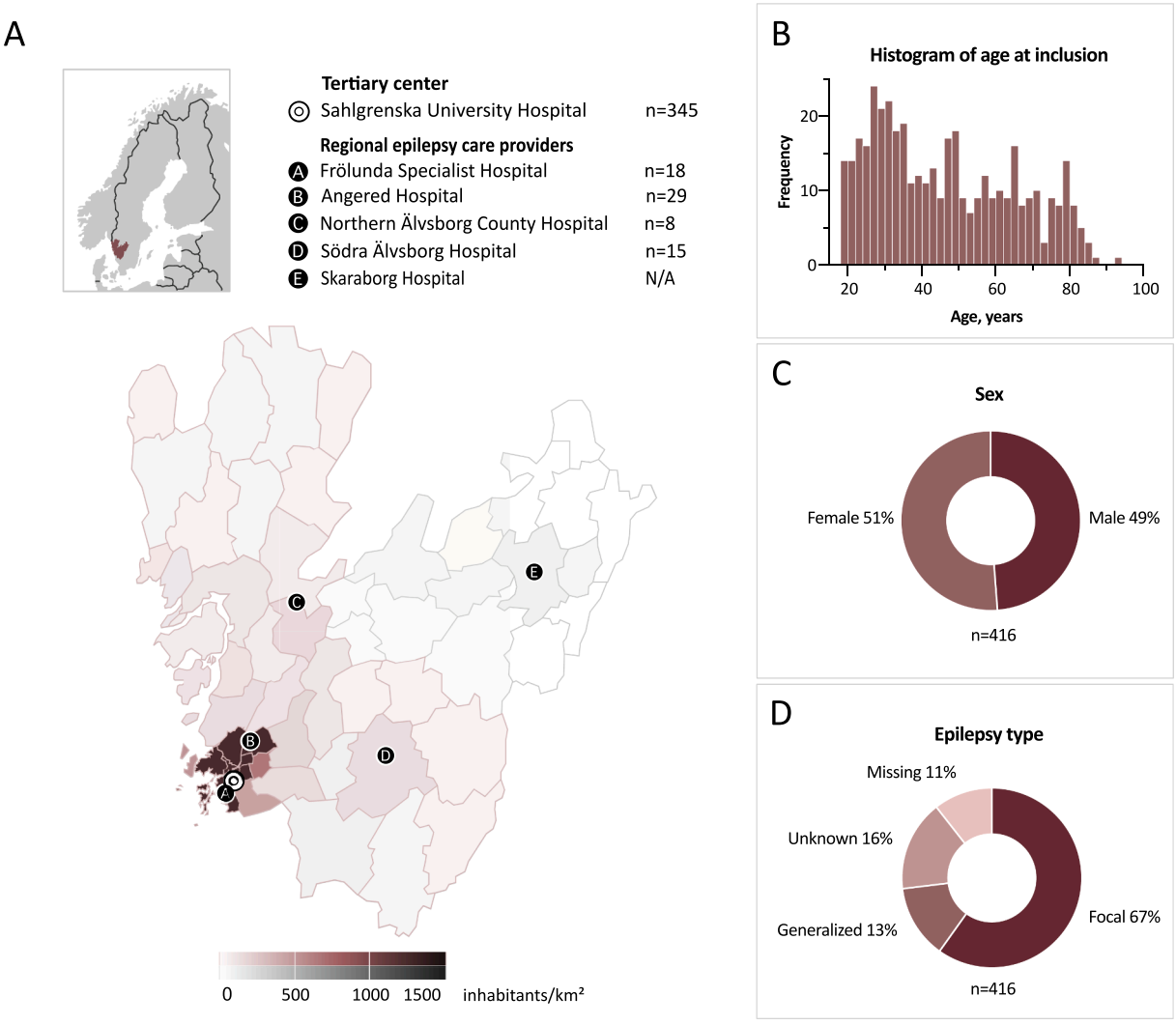

Fig. 1. (A) Map illustrating Västra Götaland County in Sweden, its municipality zones, and population density (inhabitants per square kilometre as of 2016). The public neurology units in the region are listed, along with the number of included cases per each of the five participating centres. Their catchment area is coloured in red scale, while the area of the 6th community hospital that chose not to participate is coloured in grey scale. (B) The age distribution of the 416 participants. (C) Gender distribution. (D) The participants' epilepsy types.

never, once, 2–10 times, or more than 10 times. The participants were categorized as *adherent* to ASM if they indicated forgetting their medication never or once during the past year, and *non-adherent* if they indicated forgetting their medication 2–10 times or more than 10 times. Further, information on if they had experienced seizures during the past year and whether those entailed loss of awareness, as well as presence of ASM side effects, were taken from the questionnaires.

Demographic and clinical data were retrieved from electronic medical records, by authors FA, JZ and DL. Data assessed in this study were: age, sex, whether the patients were married/with a partner or single, country of birth, driving status, type of epilepsy: focal, generalized or unknown, seizure type/-s, seizure frequency the past two months, and current ASM prescriptions. Specific ASMs prescribed to at least 5 % of the patients were included.

2.4. Statistics

Descriptive statistics are presented as median (interquartile range [IQR]) or number (%). To analyze group differences, we used the Mann Whitney's test for continuous data, and the Fisher's exact test or the χ^2 test to compare proportions. To investigate risk factors for non-adherence, logistic regression analyses were performed. Variables with a significance of $p < 0.05$ in univariable analysis were included into a multivariable stepwise analysis, retrieving the same result in stepwise forward and stepwise backward method for in- and exclusion of variables. All tests were two-sided and considered statistically significant at $p < 0.05$. Statistical analyses were performed with IBM SPSS v.29 for Windows.

2.5. Ethical approval

The Swedish Ethical Review Authority approved the study (approval no 2020-00853 with addition 2021–00257) and written consent was obtained from all participants. 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.

2.6. Data availability

Anonymized data not published within this article will be made available upon request from any qualified investigator.

3. Results

3.1. Demographic and clinical data

Four-hundred and sixteen participants were included, with a median age of 43 years, IQR 29–62. Of those, 51 % were women and 49 % were men. Their demographic and clinical data is shown in Table 1 and Fig. 1. The majority, 83 %, were recruited at the tertiary center, Sahlgrenska University Hospital. Two thirds had focal epilepsy, while 15 % had generalized epilepsy and the remainder had unknown type. For the 177 patients where the country of birth had been registered in the medical records, one fifth were born in other countries than Sweden. Concerning seizure control, there were, as stated, two applied measures: Physicians had documented seizures in the past two months in 37 % of the participants, while 52 % of the participants had themselves reported having had seizure/-s during the past year.

Eighteen patients were not under treatment with ASM at the time of completing the questionnaire. Fifteen of those had recently been diagnosed with epilepsy and had been prescribed but not yet started ASM treatment. One had prior ASM treatment, experienced a treatment gap, and was prescribed new treatment at the time of completing the questionnaire. The remaining three patients had, in a shared decision with their neurologist, decided against and were therefore not prescribed treatment for their epilepsy. Of the 398 patients under ASM at the time of inclusion, 64 % (n = 254) were on monotherapy. Certain or suspected side effects of ASM treatment were reported by 43 %. Of the 320 patients for whom driving status was commented in the medical files, 65 % had a driver's license or were practice driving.

Table 1
Demographic and clinical data.

	N of cases with data	**Patients with epilepsy** n = 416
Age, years, median (IQR)	*416*	43 (29–62)
Sex, F, n (%)	*416*	213 (51.2)
Family, partner, n (%)	*353*	204 (58)
Driver's license, n (%)	*320*	209 (65.1)
Country of birth, n (%)	*177*	
Sweden		139 (78.5)
Other European		17 (9.6)
Non-European		21 (11.9)
Epilepsy diagnosis	*372*	
Focal		249 (66.9)
Generalized		55 (14.8)
Unknown		68 (18.3)
Seizures past 2 months, n (%)	*401*	149 (37.2)
Seizures past year[1], n (%)	*410*	213 (52.0)
Loss of consciousness past year[1], n (%)	*302*	154 (51.0)
One seizure type is BTCS, n (%)	*352*	271 (77.0)
Number of current ASMs, n (%)	*416*	
0		18 (4.3)
1		254 (61.1)
2		87 (20.9)
3		48 (11.5)
4		6 (1.4)
5		3 (0.7)
Current ASM treatment, n (% of treated)		
Lamotrigine		180 (45.2)
Levetiracetam		161 (40.5)
Carbamazepine		61 (15.3)
Lacosamide		46 (11.6)
Valproate		36 (9.0)
Topiramate		36 (9.0)
Side effects[1], n (%)	*384*	166 (43.2)

[1] Patient-reported data. Abbreviations: F, female; IQR, inter-quartile range; BTCS, bilateral tonic-clonic seizure; ASM, anti-seizure medication.

3.2. Adherence

The number and proportion of patients who reported forgetting to take their ASM is shown in Fig. 2: of the 398 patients currently on ASM treatment, 48 % (n = 189) stated never having forgotten to take their ASM during the past year, 13 % (n = 51) responded that they had forgotten once, 34 % (n = 133) 2–10 times and 5 % (n = 21) of the patients indicated having forgotten more than 10 times. The remaining four patients did not respond to that question.

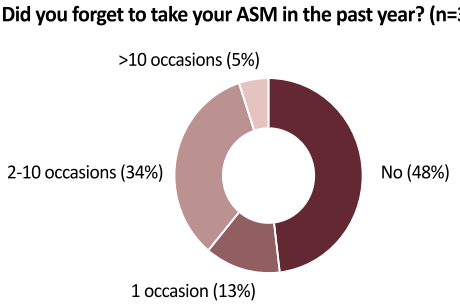

Fig. 2. The question "Did you forget to take your ASM during the past year?" was included in the participant questionnaire. The pie chart shows percentages of the participants' responses: Never, n = 189; 1 occasion, n = 51; 2–10 occasions, n = 133; >10 occasions, n = 21; Missing, n = 4.

Comparisons between *adherent* (61 %, n = 240) and *non-adherent* (39 %, n = 154) revealed that the non-adherent patients were younger, with a median age of 36 (IQR 27–50) compared to 48 (IQR 31–67) years ($p < 0.001$) (Table 2). Patients with generalized epilepsy were more often in the non-adherent group and patients with focal epilepsy were more often in the adherent group. Those who had experienced seizures the past two months or who reported seizures during the past year were to a larger extent in the adherent group, but specifically experience of loss of consciousness during the past year did not differ between the groups. Patients with side effects were over-represented in the non-adherent group, 50 % compared to 38.8 % in the adherent group ($p = 0.035$).

The number of prescribed ASMs was similar in the two groups. Of those currently on medication with levetiracetam a higher proportion were in the adherent group than in the non-adherent group (42.9 % vs 31.8 %, $p = 0.034$). Conversely, of those currently on valproate treatment, a higher proportion were in the non-adherent group (14.9 % vs 5.4 %, $p = 0.002$). The distributions of patients treated with lamotrigine, carbamazepine, topiramate, and lacosamide were similar in the two groups (Table 2).

3.3. Multivariable analysis

Age below the median age of 43 years, having a partner, a diagnosis of primary generalized epilepsy, having experienced seizures during the past two months or the past year, having a current prescription of levetiracetam or valproate and experiencing ASM related side effects were all significant factors related to adherence in univariable logistic regression analyses (Table 3). Factors that were significant in the multivariable analysis were age, self-report of seizures during the last year, valproate treatment, and self-report of side effects.

4. Discussion

A prevalence of 39 % non-adherence is lower than what has been described in many studies, and lower than the estimated average of 50 % in studies on self-reported adherence in the systematic review by Mendorf et al [10]. It is difficult to compare the statistics between studies, due to the extensive methodological variations. Adherence might be over-estimated in our study due to recall bias, as the time interval patients were asked about was as long as a year, thus perhaps contributing to the relatively low rate of non-adherence. Nonetheless, our finding illustrates a substantial potential for improvement.

Table 2
Comparisons between Adherent and Non-adherent patients.

	Adherent n = 240	Non-adherent n = 154	p
Age, years, median (IQR)	48 (31–67)	36 (27–50)	<0.001
Sex, F, n (%)	117 (48.8)	86 (55.8)	0.18
Family, partner, n (%)	123 (62.1)	69 (51.1)	0.055
Driver's license, n (%)	121 (68.8)	74 (58.7)	0.088
Country of birth, n (%)			1.0
Sweden	75 (78.1)	54 (78.3)	
Other European	10 (10.4)	7 (10.1)	
Non-European	11 (11.5)	8 (11.6)	
Follow-up at tertiary center, n (%)	198 (82.5)	128 (83.1)	0.89
Epilepsy diagnosis, n (%)			0.001
Focal	161 (73.2)	75 (57.3)	
Generalized	22 (10.0)	31 (23.7)	
Unknown	37 (16.8)	25 (19.1)	
Seizures past 2 months, n (%)	95 (40.9)	38 (25.7)	0.003
Seizures past year[1], n (%)	136 (57.4)	57 (37.5)	<0.001
Loss of consciousness past year[1], n (%)	96 (51.1)	40 (43.5)	0.25
One seizure type is BTCS, n (%)	152 (74.0)	105 (82.7)	0.079
More than one ASM, n (%)	153 (63.8)	97 (63.0)	0.92
Lamotrigine	102 (42.5)	71 (46.1)	0.53
Levetiracetam	103 (42.9)	49 (31.8)	0.034
Carbamazepine	38 (15.8)	23 (14.9)	0.89
Lacosamide	33 (13.8)	12 (7.8)	0.076
Valproate	13 (5.4)	23 (14.9)	0.002
Topiramate	20 (8.3)	16 (10.4)	0.48
Side effects[1], n (%)	90 (38.8)	75 (50.0)	0.035

[1]Patient-reported data.
Abbreviations: F, female; IQR, inter-quartile range; BTCS, bilateral tonic-clonic seizure; ASM, anti-seizure medication

4.1. Factors associated with non-adherence

A lower adherence in younger patients is well-known from other studies of long-term therapies/medications [12,13] including treatment with ASM [9,10] and was confirmed here. The reason for this lower adherence in younger patients is complex and multifactorial such as negative medication beliefs and experience of stigma [9,10,14,15]. Another suggested contributing factor is that younger persons to a larger extent live alone, also seen here: 53 % (94 of 178) of participants aged below the median of 43 years were single while 31 % (55 of 175) of those aged 43 or above were single ($p < 0.001$).

The finding that side-effects from ASMs influence adherence negatively is also well-known from other studies [9,10]. This has important clinical implications: clinicians should be aware of this issue and enquire their patients about the tolerability of the chosen drug.

The present study also showed that patients who were seizure free during the past year had a lower adherence. There are conflicting results in the literature on this topic; with 12 studies reviewed by Mendorf et al finding a higher prevalence of recent seizures in patients with low adherence [10], and other studies describing the opposite [9,16]. In any case, the finding that patients with recent seizures to a lesser extent forget their ASM is not surprising, as they will be more motivated to take their medication as prescribed. Forgetting to take ASM doses might put some of the seizure free patients at risk of break-through seizures. Although the study was not specifically designed to detect if non-adherence increased the risk of seizures, the results suggest that, on a population level, this is not the case. Nevertheless, 30 % (57 of 193) of PWE who reported having had seizures during the past year, also reported forgetting ASM doses and it is tempting to speculate that some of these cases of recent seizures were due to non-adherence.

Next, forgetting ASM doses was more common in patients with generalized epilepsy. Neuropsychological alterations in patients with idiopathic generalized epilepsy has been found in many studies, where deficits in executive function were seen in all studies, and deficits in memory functions seen in some [17]. In our stepwise statistical analysis, a diagnosis of generalized epilepsy or not was excluded from the final multivariable model. Collinearity may partly explain the finding, since there were significant associations between generalized epilepsy and younger age, valproate treatment, and with reporting freedom from seizures the past year. These three factors were all stronger risk factors for non-adherence and remained in the multivariable model after stepwise exclusion of non-significant factors. Participants with generalized epilepsy were younger, with a median age of 30 years; IQR 23–38, compared to 46 years; IQR 31–64 for those with focal, unknown or with missing epilepsy classification ($p < 0.001$). Valproate treatment was, as expected, more common in generalized epilepsy, prescribed to 18 % of patients with generalized epilepsy (10 of 55) and 7 % (26 of 361) in the remaining cohort ($p = 0.016$). Finally, participants with generalized epilepsy reported seizure freedom during the past year to a larger extent than those without generalized epilepsy: 67 % compared to 45 % (37 of 55 and 160 of 355, respectively, $p = 0.002$).

A lower adherence to valproate compared to other ASMs has been described previously. Publications by Davis et al [8] and Zeber et al [18] both investigated adherence in large cohorts of epilepsy patients by Medication Possession Ratios, MPR - meaning how many days in an observation period that drug retrievals from pharmacies will suffice for. In both studies, valproate was among the three drugs with the lowest MPR. The study by Zeber [18] selected only older patients with new-onset epilepsy. Specific epilepsy diagnosis was not accounted for, but

Table 3
Univariable logistic regression analyses of the influence of demographic and clinical factors on adherence, and the final multivariable model which includes 377 cases.

	Univariable analyses			Multivariable analysis		
	OR	95 % CI	p	OR	95 % CI	p
Age below median	2.27	1.50–3.43	<0.001	2.18	1.40–3.38	<0.001
Sex, F	1.33	0.89–2.00	0.17			
Family, partner	0.64	0.41–0.99	0.046			
Country of birth Sweden/other	1.01	0.48–2.13	0.98			
Driver's license	0.68	0.40–1-04	0.073			
Follow-up at tertiary center	0.96	0.56–1.64	0.87			
Primary generalized epilepsy	2.50	1.39–4.50	0.002			
Seizures past 2 months	0.50	0.32–0.78	0.003			
Seizures past year[1]	0.45	0.29–0.68	<0.001	0.41	0.26–0.65	<0.001
Loss of consciousness past year[1]	0.74	0.45–1.22	0.23			
Ever had BTCS	1.68	0.96–2.92	0.069			
More than one ASM	1.03	0.68–1.57	0.88			
Lamotrigine treatment	1.16	0.77–1.74	0.48			
Levetiracetam treatment	0.62	0.41–0.95	0.028			
Carbamazepine treatment	0.93	0.53–1.64	0.81			
Lacosamide treatment	0.53	0.26–1.06	0.073			
Valproate treatment	3.07	1.50–6.26	0.002	2.79	1.32–5.91	0.007
Topiramate treatment	1.28	0.64–2.55	0.49			
Side effects[1]	1.58	1.04–2.39	0.031	1.62	1.03–2.56	0.037

[1]Patient-reported data.
Abbreviations: OR, Odds ratio; CI, Confidence Interval; F, female; BTCS, Bilateral tonic-clonic seizures; ASM, Anti-seizure medication.

presumably at least the majority had focal epilepsy, meaning that the lower adherence to VPA is not only seen in generalized epilepsy. In both these studies levetiracetam and lamotrigine were the two ASMs with the highest level of adherence; in the present study, specifically levetiracetam was associated with better adherence. Levetiracetam and lamotrigine were the most commonly prescribed ASMs in this study, perhaps contributing to a comparatively low rate of non-adherence.

In contrast, another study by Bautista et al, with a smaller study group, found the opposite: old ASMs had a higher MPR compared to new ASMs [19]. Their study along with several others, also found that the number of ASMs the patients were prescribed had an inverse correlation with adherence. This could not be confirmed in our study: patients on monotherapy stated forgetting their medication to the same extent as patients with ASM polytherapy.

4.2. Limitations and strengths

The main limitation of this study is the use of just one question to assess adherence; no extensive validated questionnaire was applied. The same limitation applies for the other items in the questionnaire. The decision to use a non-validated, simple and brief questionnaire was made for the benefit of simplified inclusion of a wide range of patients, allowing for large amounts of data to be collected with minimal falling-off.

Furthermore, it is unknown what is a clinically relevant number of missed ASM doses in epilepsy. The range of having forgotten 2–10 times during one year is rough and having forgotten ASM doses twice during one year is probably not clinically relevant, but was used to capture an intermediate group between perfect and imperfect adherence.

Another limitation is that although this is a regional study, patients were mainly included at the tertiary center. Probable reasons for this are that although all neurologists at the participating centers had been informed about the study, the infrastructure and habit for including patients into research studies is more established in a university hospital. Another factor that limited the regionality of the study, was that in the two smaller neurological clinics in the Gothenburg area, patients were after inclusion by their regular neurologist asked to travel to the university hospital for blood sampling required for final inclusion, which some patients declined.

The main strength of this study is the combination of clinical data and patient reported data in a large patient cohort, with patients included in regular routine care. Many of the previous studies used solely different self-report measurements, or medication prescription data. The cohort is considered representative of epilepsy patients seen at neurology departments in Sweden and it is the first large Scandinavian patient cohort where adherence has been assessed. The age and gender distribution in the cohort is similar to that seen in Västra Götaland County and in Sweden as a whole, compared with register data from the Swedish National Board of Health and Welfare [20] (supplementary material, S2). The results should be generalizable for adult people with epilepsy living in Sweden.

This cross-sectional multicenter study found a sub-optimal adherence to ASM in 39 % of PWEs. Forgetting ASM doses was more common in the seizure free group, but was also reported by 30 % of patients with seizures during the past year. The findings can hopefully inform clinicians who treat epilepsy patients, raising awareness that younger patients, patients with side effects, and patients with valproate treatment are at higher risk of forgetting ASM doses. Structurally, the findings illustrate a need for continuous focus on fundamental aspects of epilepsy care in Sweden. The identified risk factors could enable quality improvement projects, self-management tools like smartphone apps, or improved patient education to be directed to those at risk of non-adherence.

Author contributions

KA Supervision of local inclusion, data processing, statistical analyses, interpretation of results, draft of the manuscript.

DL Data collection, interpretation of results, figure design, revision of manuscript.

FA Data collection, interpretation of results and revision of manuscript.

JZ Conceptualization of the study, supervision of inclusion and data collection, analysis planning, interpretation of results, revision of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

The Swedish Ethical Review Authority approved the study (approval no 2020-00853 with addition 2021-00257) and written consent was obtained from all participants. 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2023.100631.

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