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ORIGINAL ARTICLE

Prescribed antiseizure medication doses and their relation to defined daily doses for achieving seizure freedom in newly diagnosed patients with epilepsy

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Abstract

Objectives: To investigate the antiseizure medication (ASM) doses required to achieve seizure freedom and their correlation with the World Health Organization's defined daily doses (DDDs) in patients aged 16 years or older with newly diagnosed epilepsy.

Methods: The study included 459 patients with a validated diagnosis of new-onset epilepsy. Patient records were retrospectively analyzed to determine the ASM doses in patients with or without seizure freedom during follow-up. The DDD of the relevant ASM was then retrieved.

Results: The seizure-freedom rate with first and subsequent ASMs was 88% (404/459 patients) during the follow-up. The mean prescribed doses (PDDs) and PDD/DDD ratio of the most commonly used ASMs, ie, oxcarbazepine (OXC), carbamazepine (CBZ), and valproic acid (VPA), differed significantly between seizure-free and non-seizure-free status (992 mg and 0.99 vs 1132 mg and 1.13; 547 mg and 0.55 vs 659 mg and 0.66; and 953 mg and 0.64 vs 1260 mg and 0.84, respectively). The effect of the OXC dose as the first failed ASM on the possibility of achieving seizure freedom was significant (Fisher's exact test, $p = 0.002$). Thirty-four of 43 patients (79%) in which an OXC dose of ≤900 mg failed became seizure-free, as compared with 24 of 54 patients (44%) with a failed OXC dose >900 mg.

Significance: The present study provides new insights into the doses of the commonly used ASMs such as OXC, CBZ, and VPA that can lead to seizure freedom as monotherapy or as combination therapy. The higher PDD/DDD ratio of OXC (0.99) than that of CBZ or VPA renders a generalized PDD/DDD comparison highly problematic.

KEYWORDS

antiseizure medication, defined daily dose, newly diagnosed epilepsy, oxcarbazepine, seizure freedom, treatment outcomes

1 | INTRODUCTION

Using antiseizure medications (ASMs) to treat epilepsy in newly diagnosed patients requires careful consideration of patients' risk factors and drug-dosing requirements, based on age and additional factors, with seizure freedom as the ultimate goal.[1] As new ASMs emerge, the potential for rational prescription of ASMs by physicians has become increasingly challenging.[2] Furthermore, if seizure freedom is not obtained with the first ASM, the proliferation of possibilities for subsequent trials of ASMs, either as monotherapy or combination therapy, further complicates the potential for safe and effective practice.[3]

To compare drug consumption between different periods and/or regions, the World Health Organization (WHO), in 1996, launched a methodology for defining daily doses, which refer to the assumed average maintenance dose per day of a drug used for its main indication in adults.[4] The application of defined daily doses (DDDs) by medical professionals allows the measurement of changes over time when using a particular drug and for the evaluation of the effectiveness of different classes of drugs used in patients. DDDs have been assigned to ASMs that are used in combination therapies. While the DDD represents a unit of drug consumption, it often reflects the dosage in the context of monotherapy.[4] For example, ASM utilization in Israel was reported as DDD/1,000 inhabitants per day for a given drug,[5] and another recent study registered the prescribed drug doses (PDDs) as well as the PDD/DDD ratio for the evaluation of ASM prescription patterns and dosing.[6] Additionally, the DDD concept has been used to represent the total ASM load to allow for comparison with the ever-increasing number of ASMs in combination therapy.[7] Furthermore, the DDD has been applied to estimate the population-attributable risk of negative outcomes of drug treatment for various indications, such as hip fractures associated with diazepam or anti-depressant use.[8,9]

Importantly, after the release of the International League Against Epilepsy (ILAE) guidelines for the definition of drug-resistant epilepsy,[10] the DDD has been used to operationalize an adequate dose for ASM trials. Based on one study, it has been suggested that a PDD value that is 75% of the DDD may be sufficient for achieving seizure freedom and therefore could be applied as a measure of an adequate ASM trial in this context.[11] Using a 75% threshold as a measure for achieving seizure freedom was supported by a cross-sectional study.[12]

It is difficult to define the clinically effective dose range for each individual ASM rigidly. This is further confounded by the setting in which the ASM is used (eg, monotherapy or polytherapy). Moreover, dose optimization is a slow and complex process involving both subjective and objective factors including individual physician's own clinical evaluation based on personal experience as well as specific patient-related aspects such as epilepsy type and comorbidities. To ensure generalizability from a given ASM to another, an easier reference may be made to the DDD.[10] Due to the potential discrepancies between doses used in combined therapy and DDDs derived from monotherapy contexts, monitoring PDDs and comparing them with DDDs can have implications for doses used to achieve optimal outcomes in patients with epilepsy.[13] To complicate matters further, there is some evidence that certain duotherapies, such as lamotrigine (LTG) combined with valproic acid (VPA), may work synergistically to provide superior seizure control than achieved with each drug independently. In a previous study, it was noted that the mean daily doses of combined LTG–VPA were significantly lower in patients with improved seizure frequency than in those who received monotherapy.[14] These data about LTG–VPA highlight the importance of both pharmacokinetic[15] and pharmacodynamic interactions.[16] Therefore, the variability of doses for a single ASM using polytherapy, depending on other ASMs, may complicate comparisons with both monotherapy and combination therapy doses of the drugs, causing further heterogeneity when using DDD as a unit of ASM load measurement.

The main purpose of this study was to evaluate the required ASM doses for achieving seizure freedom in monotherapy or polytherapy and their correlation with the WHO's DDD in patients aged 16 years or older with newly diagnosed epilepsy. No previous study has investigated

Key Points

- The seizure-freedom rate with first-line and subsequent ASMs was 88%
- We defined the mean PDDs and PDD/DDD ratios of the most commonly used ASMs in both 1-year seizure-free and non-seizure-free patients
- A dose of ≤900 mg OXC as first-line ASM predicted seizure-freedom with any subsequent ASM
- The PDD/DDD ratio for seizure-free patients was 0.99 OXC whereas the ratio was 0.55 for CBZ and 0.64 for VPA
- The mean dose of LTG for achieving seizure freedom was 189 mg when used as first-line monotherapy or 97 mg in combination therapy with VPA

the DDDs in the context of polytherapy or the PDD/DDD ratio of various ASMs.

2 | METHODS

A total of 584 patients aged 16 years or older were referred to the Tampere University Hospital between January 1, 1995, and December 31, 2005, following a diagnosis of new-onset epilepsy. All individuals were retrospectively followed-up until they had been seizure-free for at least 1 year; until December 31, 2006; or until death. Medical records were retrospectively examined. The study cohort comprised 459 patients with validated newly diagnosed epilepsy, with the epilepsy type and etiology as described in detail in our previous publications.[17,18] ASM therapy was initiated according to standard clinical practice during that period. If seizure freedom was not achieved with the initial dose, the dose of the first ASM was increased or substitution/add-on ASMs were initiated at the treating physician's discretion, reflecting decision-making in a real-world context. ASM doses were adjusted according to the dictated clinical circumstances, with particular attention given to efficacy and tolerability.

In epilepsy, the DDD for different ASMs are as follows: diazepam 10 mg; carbamazepine (CBZ), 1000 mg; clobazam, 20 mg; clonazepam, 8 mg; gabapentin, 1800 mg; LTG 300 mg, levetiracetam (LEV) 1000 mg; oxcarbazepine (OXC), 1000 mg; phenytoin, 300 mg; phenobarbital, 100 mg; pregabalin, 300 mg; topiramate, 300 mg; tiagabine, 30 mg; and VPA, 1500 mg.[19]

Absolute dose sizes and ratios of PPD and DDD are described as means with ranges and medians with interquartile ranges. Comparisons between different groups were performed using the Mann–Whitney *U*-test. The data were analyzed using Stata version 16.1 (StataCorp LLC).

In this retrospective study, there was no contact with patients, and information was collected from the patient register of the Tampere University Hospital. This study does not require ethics committee approval according to Finnish Law on Research. Following Finnish guidelines, this study was approved by the head of the Tampere University Science Center.

3 | RESULTS

The clinical characteristics of all 459 patients with validated, newly diagnosed epilepsy, who remained in this study cohort, have been presented in detail in our previous publications.[17,18] The combined seizure-freedom rate with firstfirst and subsequent ASMs was 88.0% (404 of 459), and all patients with generalized epilepsy became seizure-free following the administration of a second or subsequent ASM. Among patients who achieved 1-year seizure freedom in the entire cohort, 10.1% (41 of 404) were on combination therapy. In total, 70 different ASM monotherapies or polytherapies (ASM combinations) were used.[18] In Table 1, the clinical characteristics of patients who became seizure-free with the first or subsequent monotherapy or combination therapy are compared with those of patients who did not achieve seizure freedom. Those ASMs used by less than 40 patients were excluded from this and subsequent Tables and statistical analysis: topiramate ($N=31$), phenytoin ($N=27$), gabapentin ($N=19$), tiagabine ($N=14$), clobazam ($N=11$), clonazepam ($N=8$), diazepam ($N=2$), pregabalin ($N=2$), and phenobarbital ($N=1$).

A comparison of the PDD and PDD/DDD ratio was made for all ASMs used, whether in monotherapy or in combination therapy (Table 2). The results were analyzed for focal epilepsy because of the limited number of patients with generalized epilepsy. OXC, CBZ, and VPA demonstrated statistically significant differences in terms of mean prescribed doses and PDD/DDD ratio between patients with 1-year seizure-free and non-seizure-free status (992 mg and 0.99 vs 1132 mg and 1.13; 547 mg and 0.55 vs 659 mg and 0.66; and 953 mg and 0.64 vs 1260 mg and 0.84), respectively. Remarkably, the PDD/DDD ratio for seizure-free patients was 0.99 OXC whereas the ratio was 0.55 for CBZ and 0.64 for VPA. There was no difference in VPA dosing between seizure-free patients with focal or generalized epilepsy (the mean dose of VPA for seizure-free patients with generalized epilepsy was 924 mg and those not achieving seizure freedom 1,200 mg). The only third-generation ASM widely used in patients with focal epilepsy was LTG.[20] More than 40 patients used LTG, with an absolute mean dose of 248 mg for seizure-free patients and a PDD/DDD ratio of 0.83.

Table 3 summarizes the PPDs and DDDs of the first ASM and first substitution/subsequent monotherapy ASM in all patients with epilepsy. No statistically significant differences in doses were observed, regardless of whether the drugs were used as first-line epilepsy treatment or as a first or subsequent substitution. The doses and PDD/DDD ratios for the most used ASMs (OXC, CBZ, and VPA) were comparable with the doses in Table 2. Only LTG, which was initiated seldom as the first monotherapy, had a lower mean dose and PDD/DDD ratio (189 mg and 0.63, respectively) than in all patients with LTG (including also polytherapy usage).

Table 4 presents the ASM mean PDDs and PDD/DDD ratio analysis in patients with focal epilepsy on polytherapy, demonstrating that patients achieving seizure-freedom with OXC as part of combination therapy had a higher dose of OXC than patients who used it as a

TABLE 1 Clinical characteristics of the study group categorized based on seizure outcomes

	1. All seizure-free patients	1A. Seizure-free after 1st ASM	1B. Seizure-free after 2nd or later monotherapy	1C. Seizure-free with polytherapy	2. Persistent seizures
n	404	308	55	41	55
Sex, *n* (%)					
Female	179 (44.3)	125 (40.6)	33 (60.0)	21 (51.2)	29 (52.7)
Male	225 (55.7)	183 (59.4)	22 (40.0)	20 (48.8)	26 (47.3)
Age at date of diagnosis, med (IQR)	46.0 (31.5)	45.5 (31.0)	52.0 (36.0)	36.0 (31.0)	42.0 (24.0)
Etiology, *n* (%)					
Structural	203 (50.2)	147 (47.5)	31 (56.4)	25 (61.0)	38 (69.1)
Genetic	25 (6.2)	18 (5.8)	1 (1.8)	6 (14.6)	0
Infectious	12 (3.0)	9 (2.9)	2 (3.6)	1 (2.4)	3 (5.5)
Unknown	164 (40.6)	134 (43.5)	21 (38.2)	9 (22.0)	14 (25.5)
Epilepsy type, *n* (%)					
Focal	379 (93.8)	290 (94.2)	54 (98.2)	35 (85.4)	55 (100)
Generalized	25 (6.2)	18 (5.8)	1 (1.8)	6 (14.6)	0
ASM					
Carbamazepine, *n* (%)	72 (17.8)	54 (17.5)	10 (18.2)	8 (19.5)	9 (16.4)
Lamotrigine, *n* (%)	47 (11.6)	12 (3.9)	15 (27.3)	20 (48.8)	20 (36.4)
Levetiracetam, *n* (%)	26 (6.4)	4 (1.3)	4 (7.3)	18 (43.9)	17 (30.9)
Oxcarbazepine, *n* (%)	258 (63.9)	184 (59.7)	44 (80.0)	30 (73.2)	49 (89.1)
Valproic acid, *n* (%)	98 (24.3)	51 (16.6)	34 (61.8)	13 (31.7)	17 (30.9)

Note: Patients achieving seizure freedom during follow-up were further subdivided to those becoming seizure free after first ASM regimen (1A), second or later monotherapy regimen (1B) and with any polytherapy (1C).

Abbreviations: ASM, antiseizure medications; IQR, interquartile range; med, median.

TABLE 2 PDDs of ASMs and PDD/DDD ratio in all patients including mono- and polytherapy based on seizure outcome status

	Seizure-free					Not seizure-free					
		Absolute dose in mg		PDD / DDD			Absolute dose in mg		PDD / DDD		
	n	Mean (sd)	Med (IQR)	Mean (sd)	Med (IQR)	*n*	Mean (sd)	Med (IQR)	Mean (sd)	Med (IQR)	*p*
Focal epilepsy											
OXC	213	992 (402)	900 (600)	0.99 (0.40)	0.90 (0.60)	92	1132 (507)	900 (900)	1.13 (0.51)	0.90 (0.90)	0.047
CBZ	58	547 (258)	400 (200)	0.55 (0.26)	0.40 (0.20)	22	659 (258)	600 (400)	0.66 (0.26)	0.60 (0.40)	0.031
VPA	64	953 (395)	950 (400)	0.64 (0.26)	0.63 (0.27)	30	1260 (658)	1000 (900)	0.84 (0.44)	0.67 (0.60)	0.021
LTG	30	248 (148)	200 (300)	0.83 (0.49)	0.67 (1.00)	31	285 (164)	300 (250)	0.95 (0.55)	1.00 (0.83)	0.343
LEV	17	1441 (827)	1000 (1000)	0.96 (0.55)	0.67 (0.67)	22	1650 (851)	1250 (1500)	1.10 (0.57)	0.83 (1.00)	0.337

Note: *p* = Mann–Whitney *U*-test between seizure-free and not seizure-free.

Abbreviations: CBZ, Carbamazepine; DDD, defined daily dose; IQR, interquartile range; LEV, Levetiracetam; LTG, Lamotrigine; med, median; OXC, Oxcarbazepine; PDD, prescribed daily dose; sd, standard deviation; VPA, Valproic acid.

monotherapy: 1,413 mg, with a high-PDD/DDD ratio of 1.41. The mean OXC doses and PDD/DDD ratio were somewhat, but not significantly, higher for non-seizure-free patients (1588 mg, 1.50, respectively). The number of patients taking CBZ or VPA in polytherapy was too low to draw any conclusions. Among the third-generation ASMs, there were sufficient numbers of polytherapy patients using LEV for meaningful analysis: there was no

TABLE 3 PDD ASM doses and PDD/DDD ratio in all patients either achieving seizure freedom or not with the first or subsequent monotherapy

		1st ASM					1st or subsequent substitution				
			Absolute dose in mg		PDD/DDD			Absolute dose in mg		PDD/DDD	
		n	mean (range)	med (IQR)	mean (range)	med (IQR)	*n*	mean (range)	med (IQR)	mean (range)	med (IQR)	*p*
OXC	SF	184	949 (300–2700)	900 (600)	0.95 (0.30–2.70)	0.90 (0.60)	9	900 (600–1500)	900 (0)	0.90 (0.60–1.50)	0.90 (0)	0.861
	NSF	50	867 (300–1800)	900 (300)	0.87 (0.30–1.80)	0.90 (0.30)	9	950 (600–1800)	750 (600)	0.95 (0.60–1.80)	0.75 (0.60)	0.698
CBZ	SF	54	554 (400–1800)	400 (200)	0.55 (0.40–1.80)	0.40 (0.20)	0					-
	NSF	17	562 (400–1050)	400 (300)	0.56 (0.40–1.05)	0.40 (0.30)	2	400 (200–600)	400 (400)	0.40 (0.20–0.60)	0.40 (0.40)	0.573
VPA	SF	50	932 (400–2000)	900 (400)	0.62 (0.27–1.33)	0.60 (0.27)	21	914 (600–1800)	1000 (400)	0.61 (0.40–1.20)	0.67 (0.27)	0.835
	NSF	9	900 (300–1800)	1000 (400)	0.64 (0.20–1.20)	0.67 (0.40)	9	989 (600–1500)	1000 (600)	0.66 (0.40–1.00)	0.67 (0.40)	0.563
LTG	SF	9	189 (100–400)	200 (100)	0.63 (0.33–1.33)	0.67 (0.33)	9	239 (100–400)	200 (100)	0.80 (0.33–1.67)	0.67 (0)	0.279
	NSF	4	213 (50–400)	200 (175)	0.71 (0.17–1.33)	0.67 (0.58)	11	264 (100–500)	200 (200)	0.88 (0.33–1.67)	0.67 (0.67)	0.571
LEV	SF	1	1000 (1000–1000)	1000 (0)	0.67 (0.67–0.67)	0.67 (0)	3	833 (500–1000)	1000 (500)	0.56 (0.33–0.67)	0.67 (0.33)	1.000
	NSF	0					2	1750 (1000–2500)	1750 (1500)	1.17 (0.67–1.67)	1.17 (1.00)	-

Note: p = Mann–Whitney U-test between 1st ASM and 1st or subsequent monotherapy.

Abbreviations: ASM, antiseizure medications; 1st ASM, first ASM regimen; 1st or subsequent substitution, second or later ASM regimen; CBZ, Carbamazepine; DDD, defined daily dose; IQR, interquartile range; LEV, Levetiracetam; LTG, Lamotrigine; med, median; NSF, not seizure-free; OXC, Oxcarbazepine; PDD, prescribed daily dose; SF, seizure-free; VPA, Valproic acid.

significant difference in patients with or without seizure freedom (dose and PDD/DDD ratio: 1615 mg and 1.081 vs 1800 and 1.20, respectively). (Table 4). Overall, 13 patients received LTG in combination with VPA. Of those, 4 became seizure-free with a low dose of LTG (dose and PDD/DDD ratio: 94 mg and 0.31, respectively). Nine patients did not achieve seizure freedom with a mean LTG dose of 303 mg (PDD/DDD ratio: 1.01) (Table 5).

Finally, we analyzed the value of the OXC dose as the first failed monotherapy for predicting the likelihood of achieving seizure freedom with subsequent ASM regimens during the follow-up period. There were 281 patients who used OXC as the first ASM, including 97 who did not achieve seizure freedom with OXC. During the follow-up, 59 of these 97 patients (60.8%) became seizure-free with any subsequent ASM regimen. When addressing the dose of OXC as a failed first ASM categorized into 3 different levels 300–600 mg, 900 mg, or 1,050–2,400 mg with the PDD/DDD ratios up to 0.60 or 0.90 and more than 0.90, the effect of the dose of OXC as the first failed ASM on the possibility of achieving seizure-freedom was significant (Fisher's exact test, $p = 0.002$). Thirty-four of 43 patients (79%) in whom first-line OXC failed to achieve seizure freedom at a dose of 900 mg or lower subsequently became seizure free, as compared with 24 of 54 patients (44%) in whom first-line OXC at a dose of more than 900 mg was unsuccessful (Figure 1).

4 | DISCUSSION

The present study provides new insights into doses for different ASMs, particularly OXC, CBZ, and VPA, as first-line or subsequent monotherapy, as well as in combination therapy, that resulted in seizure freedom in patients with newly diagnosed epilepsy. We identified marked variation in the ratio of the PDD to DDD, which renders a general PDD/DDD comparison highly problematic, particularly for OXC. Finally, we demonstrated that failure of OXC, the most-prescribed ASM, as the first-line monotherapy at a dose of ≤900 mg was predictive of achieving seizure freedom with subsequent ASMs.

We were able to offer a highly representative analysis for OXC given its use as the most commonly selected first-line ASM for focal epilepsy (305 patients in our study). The significant findings included the observation that, in focal epilepsy, a median dose of 900 mg of OXC as monotherapy was registered for seizure freedom, whereas in the polytherapy context, the median dose for seizure freedom was 1500 mg. In previous studies, the OXC dose was variable. In a Chinese study of newly diagnosed focal epilepsy patients, 62 out of 102 patients treated with OXC as the first choice became seizure-free with either 600 or 900 mg

TABLE 4 Seizure outcomes and antiseizure medication doses for all medications used in polytherapy (excluding valproate acid and lamotrigine combination) in patients with focal epilepsy.

	Prescribed dose in mg						PDD/DDD						
	Seizure-free			Not seizure-free			Seizure-free			Not seizure-free			
	n	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*p*
OXC	19	1413 (462)	1500 (600)	34	1588 (316)	1500 (450)	19	1.41 (0.46)	1.50 (0.60)	34	1.59 (0.32)	1.50 (0.45)	0.322
CBZ	3	533 (115)	600 (200)	5	950 (229)	800 (400)	3	0.53 (0.12)	0.60 (0.20)	5	0.95 (0.23)	0.80 (0.40)	0.036
VPA	3	867 (231)	1000 (400)	7	1300 (698)	1500 (1400)	3	0.58 (0.15)	0.67 (0.27)	7	0.87 (0.47)	1.00 (0.93)	0.490
LTG	7	371 (170)	500 (300)	9	328 (160)	300 (300)	7	1.24 (0.57)	1.67 (1.00)	9	1.09 (0.53)	1.00 (1.00)	0.541
LEV	13	1615 (870)	1000 (1000)	16	1800 (894)	1750 (1750)	13	1.08 (0.58)	0.67 (0.67)	16	1.20 (0.60)	1.17 (1.17)	0.486

Note: *p* = Mann–Whitney *U*-test between seizure-free and not seizure-free.

Abbreviations: CBZ, Carbamazepine; DDD, defined daily doses; IQR, interquartile range; LTG, Lamotrigine; LEV, Levetiracetam; med, median; OXC, Oxcarbazepine; PDD, prescribed drug doses; VPA, Valproic acid.

TABLE 5 Seizure outcomes and antiseizure medication doses for lamotrigine in combination with valproic acid in focal epilepsy

	Absolute dose in mg					PDD/DDD						
	Yes			No		Yes			No			
	n	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*p*
VPA	4	1325 (822)	1100 (1050)	9	1500 (650)	1500 (800)	4	0.88 (0.55)	0.73 (0.70)	9	1.00 (0.43)	1.00 (0.53)	0.613
LTG	4	94 (43)	88 (63)	9	303 (182)	300 (300)	4	0.31 (0.14)	0.29 (0.21)	9	1.01 (0.61)	1.00 (1.00)	0.053

Note: *p* = Mann–Whitney *U*-test between seizure-free and not seizure-free.

Abbreviations: DDD, defined daily doses; IQR, interquartile range; LTG, lamotrigine; PDD, prescribed drug doses; sd, standard deviation; VPA, valproic acid.

of the drug, whereas only 10% of the patients with OXC were titrated to doses over 900 mg.[21] In our previous study from Tampere, 80% of patients became seizure-free with OXC as the first-line ASM with doses ≤900 mg, whereas 20% of patients achieved seizure-freedom with doses of 1200 mg or 1500 mg.[22]

The 2nd and 3rd most commonly used ASMs in our study were CBZ and VPA, respectively, accounting for 80 and 94 patients, respectively. In patients with focal epilepsy, the mean dose of the ASM for achieving seizure freedom was 547 mg for CBZ and 953 mg for VPA, whereas in patients who did not achieve seizure freedom, the doses were slightly but significantly higher (659 mg and 1260 mg, respectively). These doses were comparable to those previously published.[23] The number of patients treated with CBZ or VPA as part of polytherapy was too small to draw conclusions. Furthermore, the mean dose of LTG for achieving seizure freedom (248 mg) was comparable with previously reported data, with lower doses when used as first-line monotherapy (189 mg) or in combination therapy with VPA (97 mg).[23] The number of patients using third-generation ASMs in our study was too small to allow firm conclusions, particularly regarding monotherapy. However, LEV was the second most-commonly used ASM in polytherapy (29 patients), with a mean daily dose of 1615 mg in patients who became seizure-free and 1800 mg in those who did not become seizure-free.

The PDD/DDD ratios of the most-commonly used ASMs in patients with focal epilepsy in our study varied significantly, with a mean seizure-freedom PDD/DDD ratio of 0.99 for OXC, 0.55 for CBZ, and 0.64 for VPA. For all ASMs, the PDD/DDD ratios were higher when seizure freedom was not achieved. The high-mean PDD/DDD ratio for OXC compared to those for CBZ and VPA signifies that the DDD-based comparison is not valid when OXC is part of the ASM equation. Brodie et al. previously speculated about the outlier status of OXC questioning the WHO-defined DDD for CBZ and OXC, which were both assigned the same DDD (1000 mg/day), since a dose ratio of 1:1.5 for CBZ vs OXC is often assumed in clinical practice and in research.[11] Our study now provides data to support the aforementioned notion. Moreover, in a Hungarian cross-sectional study, the mean PDD/DDD ratio for OXC in seizure-free patients was only slightly lower than that noted in our patients.[12] Additionally, the mean PDD/DDD ratios for achieving seizure freedom with CBZ and VPA in our study were in line with those reported in previous studies.[11,12] The outlier values for OXC also implies that the 75% DDD dose as a definition of an adequate ASM trial cannot be applied to OXC. Conversely, the significance of an OXC dose of ≤900 mg as the first failed monotherapy for predicting an increased possibility of seizure freedom for subsequent ASMs was in line with reported outcomes for other ASMs, such as CBZ, VPA, and LTG.[11]

Pharmacokinetic interactions between ASMs complicate the assessment of dosing further in polytherapy settings in our study. CBZ is strong inducer of cytochrome P450 and glucuronizing enzymes whereas OXC has weaker inducing properties, and a lower propensity to cause interactions mediated by enzyme induction. Conversely, enzyme inhibitors such as VPA result in decreased metabolic clearance of the affected drug, such as LTG and CBZ.[15] Furthermore, different combinations of ASMs may produce either increased (synergism) or decreased (antagonistic) efficacy or tolerability.[16]

Owing to the retrospective study design, selection bias is a potential limitation of this study. Especially, dose optimization is dependent on the complex set of clinical and physician-derived variables which are difficult to operationalize. The small sample size for some ASMs in this cohort limited the potential for statistical analysis of seizure-freedom status. In addition, our cohort consisted

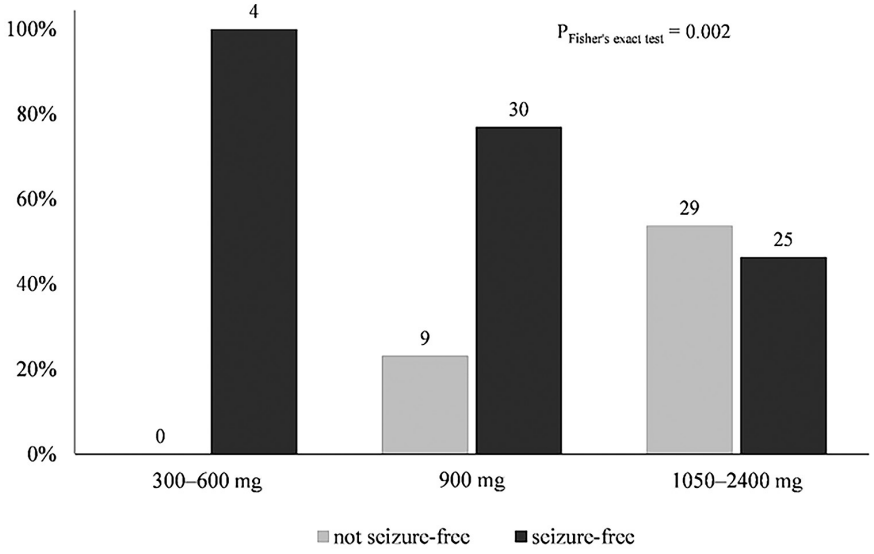

FIGURE 1 The predictive value of OXC dose as the 1st failed monotherapy for possibility of seizure freedom with subsequent ASM regimens.

of patients from an era when newer ASMs were not yet widely used. However, due to the reimbursement policy in Finland, CBZ, OXC, and VPA are currently chosen as the first-line treatment. ASMs for focal epilepsy in Finland and many newer ASMs are reimbursed only when they are used as an add-on therapy, but not as a substitution therapy. Nevertheless, the new ASMs have not yet improved the probabilities of seizure freedom.[24,25] Because of our study design, an initial seizure-freedom rate of at least 1 year was used; however, long-term seizure-freedom rates were not available. We were unable to document possible underreporting of seizures. The low proportion of focal impaired awareness seizures in our cohort may also be due to a lack of recognition of these seizures, as previously described.[26]

In conclusion, the present study provided new insights into the doses of the commonly used ASM, OXC, that leads to seizure freedom in patients with newly diagnosed epilepsy when used as first-line or subsequent monotherapy, as well as when used in combination therapy. We demonstrated marked variation in the ratio of PDDs to DDDs, rendering a generalized PDD/DDD comparison highly problematic, for OXC in particular, but also for LTG as first-line monotherapy or in combination therapy with or without VPA. Finally, for OXC, we demonstrated the value of a dose of ≤900 mg of OXC as first failed monotherapy for predicting achievement of seizure freedom, suggesting a decision-point dose for an adequate trial of OXC for ILAE definition.

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CONFLICT OF INTEREST STATEMENT

H.H., J.T.S., and J.R. report no conflicts of interest. J.P. has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from Angelini Pharma, LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for Angelini Pharma, Jazz Pharma, Novartis, LivaNova, Eisai, Medtronic, UCB, and Pfizer. 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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