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ORIGINAL ARTICLE

Treatment outcomes in women with idiopathic generalized epilepsy

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Objectives: To evaluate the changes in prescription patterns in the treatment of idiopathic generalized epilepsy (IGE) due to updated treatment recommendations and to assess seizure outcomes of valproate compared to other antiseizure medications (ASMs), with emphasis on women with epilepsy (WWE).

Materials and Methods: Records of IGE patients treated at Tampere University Hospital between 1 January 2009 and 31 December 2018 were retrospectively inspected. Data were analysed for two subgroups based on age and sex. Seizure control with reference to the efficacy of different ASMs and their combinations was examined for each subgroup.

Results: The study compiled 263 subjects (166 females and 97 males). Of all patients, 72.6% remained seizure free. There was no difference in seizure control between sexes (OR 1.25, $p = .48$). Males used valproate more often than females while females used lamotrigine and levetiracetam more often than males. Lamotrigine and levetiracetam were used especially as monotherapy in WWE, and mostly as part of combination therapy in males. Valproate alternatives were found as effective as valproate when used in monotherapy in adults. Valproate remained the most used ASM in the paediatric subgroup.

Conclusions: The use of valproate has decreased in daily clinical use with the simultaneous increased use of alternative ASMs compared to our previous study. Decreasing use of valproate in WWE did not increase the risk of seizure recurrence; therefore, valproate alternatives could be considered as first-line ASMs for WWE. Overall, IGE patients demonstrated good clinical outcomes with valproate or other broad-spectrum ASMs as monotherapy.

KEYWORDS
antiepileptic drugs, idiopathic generalized epilepsy, seizures, valproate, women with epilepsy

1 | INTRODUCTION

The most common genetic generalized epilepsy syndromes include childhood and juvenile absence epilepsies (CAE and JAE respectively), juvenile myoclonic epilepsy (JME) and generalized tonic-clonic seizures (TCS) upon awakening. In these four specific syndromes, the previously used concept idiopathic generalized epilepsies (IGE) can still be applied, according to the 2017 International League Against Epilepsy (ILAE) guidelines.[1] In addition, other less common but still clinically relevant syndromes have been included in the IGE category, such as IGE with absences of early childhood, perioral myoclonia with absences, IGE phantom absences, Jeavons syndrome (eyelid myoclonia with absences) and monogenic IGE syndromes.[2] Furthermore, the precise clinical and EEG phenotype of a single patient is often difficult to ascertain even when all information is suggestive of IGE.[3]

The main aim of epilepsy treatment is to achieve seizure freedom without adverse effects related to the medication. In general, the treatment of IGE syndromes involves the use of broad-spectrum antiseizure medications (ASM). The results from a few rigorous studies comparing outcomes with ASM for IGE have shown valproate to be the most effective ASM when treating generalized epilepsy.[4,5] However, the use of valproate has become problematic in women with epilepsy (WWE) due to its adverse effects. The European Medicines Agency (EMA) published a press release in 2014[6] and a further 2018[7] restriction advising clinicians not to prescribe valproate to women of childbearing age due to its teratogenic effects, unless other treatments fail. A joint report by the Commission on European Affairs of the International League Against Epilepsy (CEA-ILAE) and the European Academy of Neurology (EAN) in 2015 strongly agreed with previous EMA guidelines and provided further guidance on the treatment of women and girls of childbearing age with epilepsy.[8] The use of valproate during pregnancy has been connected most significantly to the risk of major congenital malformations (MCMs).[9,10] It has also been associated with lower IQ and increased risk of autism and attention deficit hyperactivity disorder in the child.[11,12] Among other broad-spectrum ASMs, lamotrigine and levetiracetam have a low risk of MCMs, and conversely, topiramate has an elevated risk of MCMs and is associated with significant growth restriction and microcephaly.[10]

There are fewer treatment options available for generalized epilepsies than for focal epilepsies. The effects of the decreased use of valproate on seizure outcomes in WWE have not been well studied.[13] Several other ASMs have been used to treat IGE, but their therapeutic potential has not been firmly established.[8] However, use of lamotrigine and levetiracetam was recommended as first-line treatments for IGE, except for CAE, for which ethosuximide is the drug of choice.[14]

Between 2005 and 2008, a single-centre follow-up study of 128 subjects with IGE was conducted at Tampere University Hospital.[15] In the current study, we evaluated whether there has been a change in the prescription patterns in the treatment of IGE due to updated treatment recommendations (with special reference to WWE) and, if so, how the reduced use of valproate[16] has affected seizure outcomes compared to those described in our previous study.[15]

2 | MATERIALS AND METHODS

2.1 | Subjects

The study was carried out at Department of Neurology, Tampere University Hospital, where all patients with epilepsy were diagnosed according to local treatment guidelines and had their treatment initiated in Pirkanmaa Hospital District (population approximately 500,000). Our department also serves as a referral centre for refractory epilepsy patients from other smaller or regional hospitals. This was an observational, noninterventional retrospective study that did not require ethics committee approval according to Finnish Law on Research. Access to patient records was based on a decision made by the Head of Science Centre, Tampere University Hospital Research and Innovation Services, Science Centre.

2.2 | Data collection

Patients with generalized epilepsy (including patients with ICD-10 codes referring to generalized epilepsy; G40.3X) who had their visit at Tampere University Hospital from 1 January 2009 to 31 December 2018 were identified from the hospital's patient registry. Patients' electronic medical records were retrospectively inspected for demographics and clinical information including age, sex, syndrome, intellectual disability (IQ < 70), time of patient's latest visit, age at diagnosis, EEG and MRI history, and complete ASM history (dosages and reasons for discontinuation). Data concerning ASM initiation and changes as well as seizure outcomes and adverse events were registered systematically. A complete seizure history was recorded for TCS, myoclonic jerks, absence seizures and unclassified seizures. The definite IGE syndromes were divided into CAE, JME, JAE and TCS. Furthermore, the possibility of other putative IGE syndromes as proposed by Panayiotopoulos in 2005[2] was assessed, and patients with eyelid myoclonia (with or without absences) but no others were found in the study group. Patients diagnosed with Unverricht-Lundborg disease, myoclonic-astatic epilepsy and Dravet syndrome were not included in this study. All the patients' diagnoses, including the cases of unclassified IGE, were re-evaluated by the investigators (RK, SR and JP) to examine whether a diagnosis of a specific syndrome could be made. If not, then the patient remained in the unclassified IGE category. The patients with unclassified IGE needed to have at least one EEG registration with generalized epileptiform activity to be classified in this category, but they did not fit into any specific generalized syndrome category. We did not include any patients with focal epileptiform activity or normal activity in this category because we only wanted to include patients with unequivocal

generalized epilepsy. They also needed to have seizure types concordant with generalized onset seizures and absence of any significant focal findings in MRI. Strict age limitations were not used, and both paediatric and adult patients were included.

Duration of seizure freedom was calculated based on the time between the patients' latest seizure (whether provoked or unprovoked) and the patients' latest visit at the neurology clinic. Seizure freedom was defined as 12 months without TCS or absence seizures or days with myoclonic jerks. Patients with a duration of epilepsy of under 12 months were excluded from calculations concerning seizure freedom as one-year seizure freedom could not be reached. The duration of epilepsy was calculated as months between the start of the patients' first medication and their latest visit at the neurology clinic. The use of different ASMs and their combinations as well as the seizure outcome were examined. The use of different ASMs was examined separately for mono- and combination therapy.

The retention rate, referring to the percentage of patients still using a specific ASM at their latest visit at the neurology clinic, was studied for each drug. The reasons for discontinuation were classified as lack of efficacy, lack of tolerability, long-term seizure freedom and other reasons. The seizure freedom for a given ASM was calculated by dividing the number of seizure-free patients using the ASM at their latest visit by the overall number of patients using the specific ASM at their latest visit. The following classifications were made for the subgroup analyses. Age (at the patients' latest visit) was categorized into two groups: paediatric (<16 years of age) and adult (≥16 years of age), and the subjects were also categorized by sex.

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

2.3 | Statistical analysis

Descriptive statistics were reported as frequencies and percentages for all variables. Pearson's chi-squared test was used to test the association between sex and the use of different ASMs. In addition, an adjusted odds ratio (OR) for the association between sex and the seizure freedom was evaluated by binary logistic regression model. We chose the factors in the model which are known to have effects on seizure outcomes. Our main question was regarding seizure freedom rates between males and females, but it is well established that epilepsy syndrome and medication selection have a major effect on the clinical outcome in terms of seizure freedom. Because of the natural evolution of generalized epilepsy, we also included the age of the patient because it does have an impact on seizure outcomes. We considered that other possible factors are probably of less importance. The association was adjusted for epilepsy syndrome, age, use of valproate, use of lamotrigine and levetiracetam at latest clinical visit. Statistical significance was defined as a p-value $< .05$, and all statistical analyses were performed with SPSS version 26.

3 | RESULTS

3.1 | Patients

Altogether, 263 subjects (166 females and 97 males) were included in the analysis. The mean age was 24.0 (range 2–81) years at the patients' latest visit and 13.3 (range 0–80) years at the start of medication. The mean duration of epilepsy for those with available data ($n = 227$) was 9.0 (range 0.4–54) years. We were unable to obtain data for 36 patients concerning the age at the start of their medication and hence the duration of their epilepsy from the electronic patient records. This was due to the patients transferring from another treatment centre or their treatment being started before the electronic registry was established. Altogether, 252 patients were included in the seizure freedom analysis because 11 patients were diagnosed less than 12 months before the latest visit at the neurology clinic. The distribution of patients based on sex, age and syndromes is presented as a flowchart of the study in Figure 1.

3.2 | Epilepsy syndromes and age-specific results

Syndrome- and age-specific results are presented in Table 1. Among all patients, 182 (72.6%) patients achieved one-year seizure freedom. Out of 15 patients with intellectual disability, only 6 (42.9%) were seizure free. There was no significant difference in multivariate analysis between the seizure freedom of male and female patients (female vs. male; OR 1.25, $p = .48$). Age or the use of a distinct ASM did not influence the outcome. Patients diagnosed with TCS only had the highest rate of seizure freedom with 81.0% ($n = 51$) seizure free at their latest visit. The proportion of seizure-free patients diagnosed with JME and CAE was similar, 75.0% ($n = 51$) and 75.8% ($n = 25$) respectively. Regarding the syndrome distribution in the entire study group, 70 (26.6%) JME, 69 (26.2%) TCS only and 51 (19.4%) unclassified IGE composed the largest syndrome diagnoses. The most common syndromes in the paediatric cohort were CAE (47.3%) followed by unclassified IGE (29.7%) and TCS only (12.2%). To compare, the most common syndromes in the adult cohort were JME (36.0%), TCS only (31.7%) and unclassified IGE (15.3%). Details for the binary logistic regression model with odds ratios for all factors used in the model are presented in the supplementary table (Table S1).

3.3 | ASMs and their efficacy

Antiseizure medications and their efficacy for the entire study group are presented in Table 2 separately for age subgroups comprising of paediatric and adult patients. In the whole study group, valproate (including both previous and present use) was the most widely used ASM ($n = 235$) in both age subgroups, followed by lamotrigine ($n = 84$) and levetiracetam ($n = 65$) (Table 3). Other drugs were used much less with 30 or less patients having used each of these ASMs

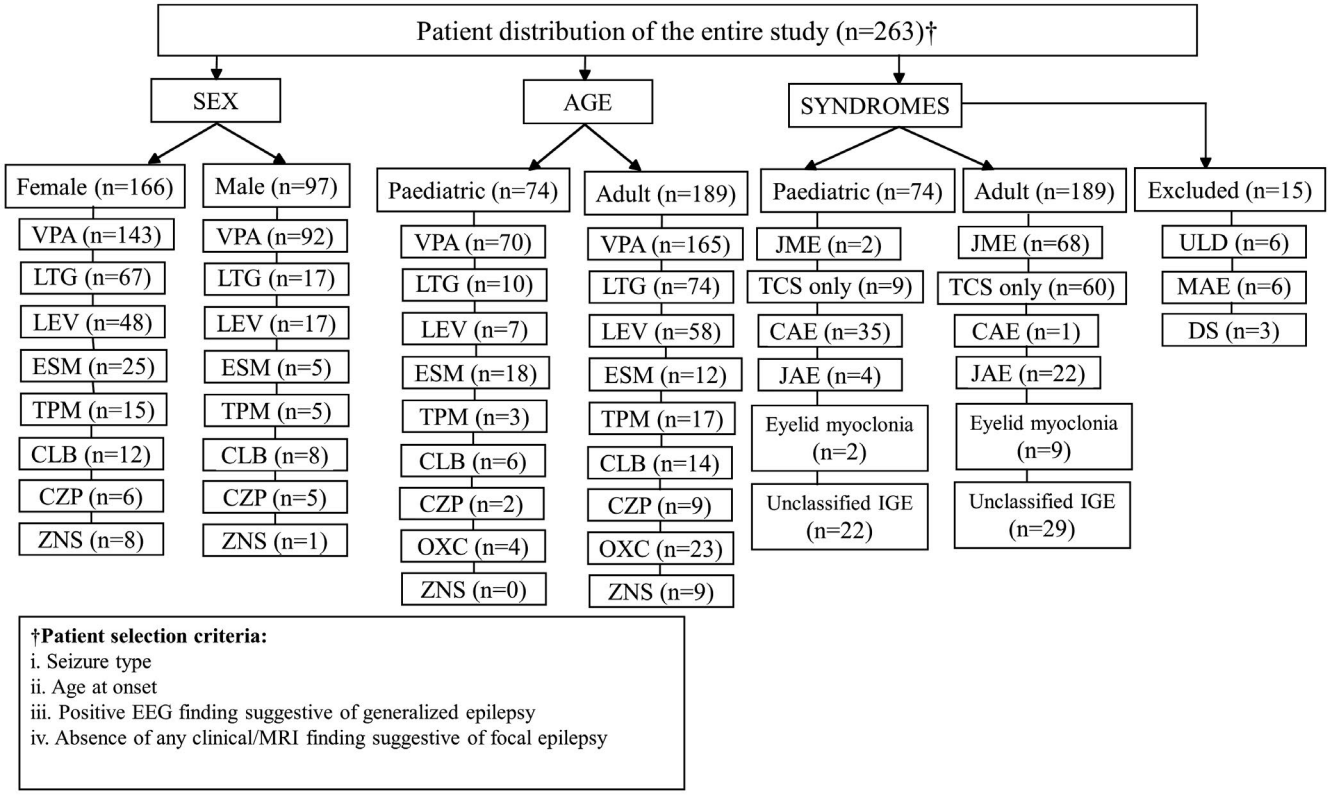

FIGURE 1 Flowchart of the study with the distribution of patients based on sex, age and syndromes. CAE, childhood absence epilepsy; CLB, clobazam; CZP, clonazepam; DS, dravet syndrome; ESM, ethosuximide; IGE, idiopathic generalized epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; LEV, levetiracetam; LTG, lamotrigine; MAE, myoclonic-astatic epilepsy; TCS, tonic-clonic seizure; TPM, topiramate; ULD, unverricht-Lundborg disease; VPA, valproate; ZNS, zonisamide

(Table 3). Although valproate was the most common drug used in both age subgroups, lamotrigine and levetiracetam were more commonly used in adults than in the paediatric population (Table 2). Phenytoin, tiagabine, phenobarbital and perampanel were also previously used by between one and six patients with no patient retaining them until their latest visit (data not shown in tables).

Next, we performed an additional analysis on seizure freedom rates based on the seizure types of patients (TCS, absence and myoclonic seizures) while using certain ASMs and their combinations (Table S2). The results showed TCS (n = 183) to be the most common seizure type, followed by absence (n = 136) and myoclonic seizures (n = 104). It is important to note down that a patient may suffer from more than one seizure type. Moreover, as monotherapy, valproate (82.8% SF) and its alternatives (80.0% SF) were almost equally efficient in treating TCS. However, valproate was found to be more efficient when treating absence (80.0% SF) and myoclonic (78.6% SF) seizures as monotherapy compared to its alternatives (56.3% SF for absence seizures and 61.5% SF for myoclonic seizures). In combination therapy, combinations including valproate were more efficient only in treating absence seizures (42.9% SF) whereas combinations without valproate were more efficient in treating TCS (57.1% SF) and myoclonic seizures (66.7% SF).

3.4 | Monotherapy and combination therapy

With 155/263 (58.9%) patients, monotherapy was the most common form of treatment, especially in paediatric patients where only 5/74 (6.8%) patients were on combination therapy at their latest visit (Table 4). Three patients using drugs which are usually not indicated for generalized epilepsy, namely oxcarbazepine and carbamazepine, were excluded from Table 4, leaving 152 patients using monotherapy on their latest visit. For comparison, with adult patients, 51/189 (27.0%) were on combination therapy at the patients' latest visits. Valproate was the most common drug used in monotherapy with 106/155 (68.4%) patients using valproate at their latest visit (Table 4). Valproate alternatives were used by 39 patients as monotherapy. More specifically, 17 patients were using lamotrigine, 18 levetiracetam, 3 topiramate and 1 patient using zonisamide as monotherapy at their latest visit (Table 3). Valproate alternatives, 29 (80.6%) patients were seizure free, were found to be as effective as valproate, and 66 (86.8%) patients were seizure free, when used in monotherapy in adult patients (Table 4). Lamotrigine was as effective as valproate when used to treat WWE in monotherapy (12 (85.7%) patients seizure free vs. 45 (80.4%) patients seizure free) (Table 3).

TABLE 1 Syndrome- and age-specific results for entire study group

	Entire study group		Paediatric					Adult					
	Total	1-year SF[a]	Total	No. of ASMs used at latest visit			1-year SF[a]	Total	No. of ASMs used at latest visit			1-year SF[a]
	N (%)	*N* (%)	*N* (%)	0	1	2	3	*N* (%)	0	1	2	3	*N* (%)
Total	263 (100)	182 (72.6)	74 (100)	35	34	4	1	49 (72.1)	189 (100)	17	121	35	16	134 (72.8)
Female	166 (63.1)	119 (73.0)	42 (56.8)	21	21	0	0	31 (75.6)	124 (65.6)	11	76	28	9	87 (72.5)
Male	97 (36.9)	64 (71.9)	34 (43.2)	14	13	4	1	18 (66.7)	65 (34.4)	6	45	7	7	46 (74.2)
JME	70 (26.6)	51 (75.0)	2 (2.7)	0	2	0	0	1 (100)	68 (36)	3	46	10	9	50 (74.6)
TCS only	69 (26.2)	51 (81.0)	9 (12.2)	7	2	0	0	7 (87.5)	60 (31.7)	4	46	10	0	44 (78.6)
CAE	36 (13.7)	25 (75.8)	35 (47.3)	15	20	0	0	25 (78.1)	1 (0.5)	0	0	1	0	0
JAE	26 (9.9)	17 (65.4)	4 (5.4)	3	1	0	0	3 (75)	22 (11.6)	3	12	5	2	14 (63.6)
Eyelid myoclonia	11 (4.2)	6 (54.5)	2 (2.7)	1	1	0	0	1 (50)	9 (4.8)	3	5	1	0	5 (55.6)
Unclassified IGE	51 (19.4)	33 (66.0)	22 (29.7)	9	8	4	1	12 (57.1)	29 (15.3)	4	12	8	5	21 (72.4)

Abbreviations: CAE, childhood absence epilepsy; IGE, idiopathic generalized epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; SF, seizure freedom; TCS, tonic-clonic seizure.

[a]Patients with a duration of epilepsy of under 12 months were excluded when calculating seizure freedom ($n = 11$).

3.5 | Sex-specific ASM use in mono- and combination therapy

ASMs used in the treatment of males and females in mono- and combination therapy are shown in Table 3. Valproate was also the most common drug used in combination therapy at the patients' latest visit ($n = 39$) with the most used combination consisting of valproate and lamotrigine ($n = 13$) (Table 4). This was closely followed by 35 patients using lamotrigine and 22 using levetiracetam as part of their combination therapy (Table 3). Valproate (73.1%, $n = 106$) and ethosuximide (54.5%, $n = 6$) were more often used as monotherapy, whereas other ASMs were more commonly used as part of combination therapy. Monotherapy was the less common form of treatment with lamotrigine and levetiracetam with 17 (32.7%) and 18 (45.0%) patients, respectively, using them as monotherapy.

Based on sex, the use of valproate at the patients' latest visit was more common in males ($n = 64$) than in females ($n = 81$) when compared in the entire study group (66.0% vs. 48.8%, $p = .007$). The use of lamotrigine and levetiracetam at the latest visit was more common in females than in males ($p = .041$ and $p = .091$ respectively). Lamotrigine was used by 39/166 (23.5%) of females and 13/97 (13.4%) of males, whereas levetiracetam was used by 30/166 (18.1%) of females and 10/97 (10.3%) of males.

This can also be observed in the female:male (F:M) ratio of these ASMs. The F:M ratio for the entire study group was 1.7:1.0. Valproate was used less often in females (F:M ratio 1.0:1.1) while lamotrigine (F:M ratio 2.3:1.0) and levetiracetam (F:M ratio 1.6:1.0) were more often used with female patients. Lamotrigine and levetiracetam were used in combination therapy especially in male patients and on the contrary as monotherapy with female patients (lamotrigine F:M monotherapy 2.7:1.0, combination therapy 1.5:1.0), (levetiracetam F:M monotherapy 2.9:1.0, combination therapy 1.3:1.0). The similar pattern of F:M ratio was not seen in the other ASMs (Table 3). Males using lamotrigine reached lower seizure freedom rates with 46.2% ($n = 6$) seizure free compared to the female subgroup with 66.7% ($n = 26$) seizure free. The proportion of overall seizure-free rates at patients' latest visit did not differ between males and females using levetiracetam (Table 3).

The most common reason for discontinuation of valproate for females was tolerability problems with 23/56 (41.0%) of patients discontinuing due to this reason (Table 2). Out of all the women who had ever been exposed to valproate, 81/143 (56.6%) patients retained valproate as their drug until their latest visit (Table 3). On the contrary, 64/92 (69.6%) of males maintained valproate use until their latest visit, and only 5/26 (19.2%) discontinuations were due to tolerability problems. Lamotrigine and levetiracetam were retained slightly better with 52/84 (61.9%) and 40/65 (61.5%) retaining them at their latest visit. Ethosuximide showed the lowest retention rate at 11/30 (36.7%) retaining the drug at their latest visit (Table 3).

Prescription patterns of different ASMs in females and males are plotted as bar charts in Figure 2A–D.

TABLE 2 All drugs ever used and their efficacy for the entire study group

	Paediatric			Adult							
	Total exposed	Retained until latest visit	SF[a]	Total exposed	Retained until latest visit	SF[a]	Reason for discontinuation n (%)				
ASMs	*N*	*N* (%)	*N* (%)	*N*	*N* (%)	*N* (%)	Tolerability	Lack of efficacy	Wrong syndrome	Long-time SF	Other
VPA	70	30 (42.3)	14 (58.3)	165	115 (69.7)	83 (74.8)	28 (34.1)	6 (7.3)	0	42 (51.2)	6 (7.3)
LTG	10	4 (40)	1 (25)	74	48 (64.9)	31 (64.6)	7 (25.9)	12 (44.4)	0	6 (22.2)	2 (7.4)
LEV	7	2 (28.6)	0	58	38 (65.5)	22 (59.5)	11 (40.7)	10 (37.0)	0	1 (3.7)	1 (3.7)
ESM	18	7 (38.9)	1 (14.3)	12	4 (33.3)	2 (50)	1 (5.9)	6 (35.3)	0	9 (52.9)	1 (5.9)
TPM	3	1 (33.3)	0	17	8 (47.1)	6 (75)	4 (44.4)	4 (44.4)	0	1 (11.1)	0
CBZ	0	-	-	17	2 (11.8)	2 (100)	2 (18.1)	2 (18.1)	3 (27.3)	3 (27.3)	1 (9.1)
CLB	6	1 (16.7)	-	14	10 (71.4)	3 (30)	2 (40.0)	3 (60.0)	0	0	0
CZP	2	0	-	9	5 (55.6)	1 (20)	2 (40.0)	2 (40.0)	0	0	1 (20.0)
OXC	4	0	-	23	4 (17.4)	1 (25)	1 (5.9)	2 (11.8)	12 (70.6)	2 (11.8)	0
ZNS	0	-	-	9	5 (55.6)	2 (40)	1 (50.0)	1 (50.0)	0	0	0

Abbreviations: CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; OXC oxcarbazepine; SF, seizure freedom; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

[a]Patients with a duration of epilepsy of under 12 months were excluded when calculating seizure freedom ($n = 11$). Seizure freedom was calculated for patients still using the drug (combination) at their latest visit.

TABLE 3 Sex-specific results for drugs use for the entire study group

			Retained until latest visit							
	Exposed overall (*n*)	Female:Male ratio	Total	Monotherapy at latest visit		Combination therapy at latest visit		Monotherapy SF at latest visit[h]	Combination therapy SF at latest visit[h]	Overall SF at latest visit[h]
ASMs	(Females 166, males 97)	(ratio in entire study group 1.7:1)	*N* (%)	*N* (%)	Female: male ratio	*N* (%)	Female: male ratio	%	%	*N* (%)
VPA	235	1:1.1	145 (61.7)	106 (73.1)	1:1.4	39 (26.9)	1:1.2	82.5	44.7	97 (71.9)
Female	143		81 (56.6)	58 (71.6)		23 (28.4)		80.4	47.8	56 (70.9)
Male	92		64 (69.6)	48 (75.0)		16 (25.0)		85.4	40.0	41 (73.2)
LTG	84	2.3:1	52 (61.9)	17 (32.7)	2.7:1	35 (67.3)	1.5:1	82.4	51.4	32 (61.5)
Female	67		39 (58.2)	14 (35.9)		25 (64.1)		85.7	56.9	26 (66.7)
Male	17		13 (76.5)	3 (23.1)		10 (76.9)		66.7	40.0	6 (46.2)
LEV	65	1.6:1	40 (61.5)	18 (45.0)	2.9:1	22 (55.0)	1.3:1	70.6	45.5	22 (56.4)
Female	48		30 (62.4)	15 (50.0)		15 (50.0)		64.3	46.7	16 (55.2)
Male	17		10 (58.8)	3 (30.0)		7 (70.0)		100.0	42.9	6 (60.0)
ESM	30	2.9:1	11 (36.7)	6 (54.5)	1.2:1	5 (45.5)	2.3:1	16.7	40.0	3 (27.3)
Female	25		8 (32.0)	4 (50.0)		4 (50.0)		0.0	50.0	2 (25.0)
Male	5		3 (60.0)	2 (66.7)		1 (33.3)		50.0	0.0	1 (33.3.)
TPM	20	1.8:1	9 (45.0)	3 (33.3)	-	6 (66.7)	1.2:1	100.0	50.0	6 (66.7)
Female	15		7 (46.7)	3 (42.9)		4 (57.1)		100.0	75.0	6 (85.7)
Male	5		2 (40.0)	0 (0.0)		2 (100.0)		-	0.0	0
CLB	20	1:1.1	11 (55.0)	1 (9.1)	-	10 (90.1)	1:1.1	0.0	33.3	3 (30.0)
Female	12		7 (58.3)	1 (14.3)		6 (85.7)		0.0	33.3	2 (28.6)
Male	8		4 (50.0)	0 (0.0)		4 (100.0)		-	33.3	1 (33.3)
CZP	11	1:1.4	5 (45.5)	0 (0.0)	-	5 (100.0)	1:6.8	-	20.0	1 (20.0)
Female	6		1 (16.7)	0 (0.0)		1 (100.0)		-	0.0	0
Male	5		4 (80.0)	0 (0.0)		4 (100.0)		-	25.0	1 (25.0)
ZNS	9	4.7:1	5 (55.6)	1 (20.0)	-	4 (80.0)	-	100.0	25.0	2 (40.0)
Female	8		5 (62.5)	1 (20.0)		4 (80.0)		100.0	25.0	2 (40.0)
Male	1		0	0		0		-	-	-

Note: Seizure freedom was calculated for the people still using the drug at their latest visit. F/M rate was corrected for the female preponderance in the cohort.

Abbreviations: CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; SF, seizure freedom; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

[a]Patients with a duration of epilepsy of under 12 months were excluded when calculating seizure freedom (SF) ($n = 11$).

TABLE 4 All drugs combinations used at patient's latest visit for the entire study group

	Total		Paediatric		Adult
			1-year SF[g]		1-year SF[g]
	N	*N*	*N* (%)	*N*	*N* (%)
0 ASM	52	35	33 (94.3)	17	13 (76.5)
1 ASM	152	34	16 (47.1)	118	98 (83.1)
VPA	106	26	14 (66.7)	80	66 (86.8)
LTG – LEV – TPM – ZNS	39	2	1 (50)	37	29 (80.6)
other[a]	7	6	1 (16.7)	1	0
2 ASMs	37	4	0	33	17 (53.1)
VPA – LTG	13	1	0	12	7 (58.3)
VPA – LEV	4	0	-	4	2 (50)
VPA – other[a]	6	2	0	4	1 (25)
LTG – LEV	6	1	0	5	4 (80)
LTG – other[b]	5	0	-	5	2 (40)
LEV – other[c]	3	0	-	3	1 (33.3)
3 ASMs	16	1	0	15	6 (40)
VPA – LTG – LEV	4	0	-	4	2 (50)
VPA – LTG – other[d]	6	0	-	6	3 (50)
VPA – LEV – other[e]	2	1	0	1	0
VPA – Other – other[f]	3	0	-	3	1 (33.3)
LEV – LTG – CLB	1	0	-	1	0

Abbreviations: CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; SF, seizure freedom; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

Seizure freedom was calculated for people still using the drug (combination) at their latest visit.

[a]CLB and ESM.

[b]CLB, CZP, ESM, ZNS.

[c]ZNS, TPM, CLB, ESM.

[d]ESM, CLB and TPM.

[e]CZP, CLB and TPM.

[f]CZP, CLB and TPM.

[g]CLB-ZNS and TPM-CZP.

[h]Patients with a duration of epilepsy of under 12 months were excluded when calculating seizure freedom (SF) ($n = 11$)

4 | DISCUSSION

Our study provides additional evidence that the decreased use of valproate does not significantly worsen seizure outcomes in WWE. This finding is important because of the widespread concerns related to the efficacy of other treatment options in IGE. Despite the still dominant use of valproate in IGE, we observed a shift in the prescription patterns of clinicians now using lamotrigine and levetiracetam also as monotherapy options for WWE. Importantly, we discovered that valproate alternatives were close to as effective as valproate when used in monotherapy to treat adults especially regarding TCS.

The one-year seizure freedom rate in patients with IGE of 72.6% in our present study is in line with our previous study.[15] Even though valproate remained the mostly used drug in the present study, there was a considerable increase in the use of valproate alternatives (lamotrigine, levetiracetam, topiramate and zonisamide). Several studies have reported the reduction in the prescription of valproate and increase in the prescription of lamotrigine and levetiracetam, especially in women of childbearing age.[16–18] It is noteworthy that valproate was more commonly used in males than females at their latest visit, suggesting that different treatment options are being considered more with WWE. The retention rate for valproate compared to our previous study was relatively lower (61.7% vs. 84% respectively). Most likely, clinicians are currently more inclined to change the treatment regimen from valproate to its alternatives than they previously were due to increasing data supporting the efficacy of other ASMs, as well as the publication of new guidelines recommending against the usage of valproate with WWE.

In the present study, the use of lamotrigine and levetiracetam had increased and the use of valproate decreased in the treatment of IGE compared to our previous study.[15] This suggests that in WWE, lamotrigine and levetiracetam are also used as monotherapy options; conversely, in males, valproate remains the monotherapy option,

FIGURE 2 Prescription patterns of different ASMs in females and males. (A) Proportion of patients exposed to certain ASMs at their latest visit, (B) seizure freedom rates for patients using certain ASMs at their latest visit, (C) distribution of female patients using certain ASMs as mono- and combination therapy and (D) distribution of male patients using certain ASMs as mono- and combination therapy. ASMs, antiseizure medications; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate; VPA, valproate; ZNS, zonisamide

and lamotrigine and levetiracetam are used mainly in combination therapies. Despite the differences found in the use of valproate and its alternatives between female and male patients, no significant difference was found in seizure control between them, suggesting that valproate alternatives may be efficacious as monotherapy treatment options. When comparing the efficacy of ASMs used in treating WWE in monotherapy, lamotrigine even reached a higher rate of seizure freedom compared to valproate. Thus, our study suggests that valproate and its alternatives have similar efficacy, especially when used in monotherapy to control TCS; however, valproate was more efficacious when treating myoclonic and absence seizures.

Unfortunately, there are still only a few randomized controlled trials examining generalized epilepsy.[19] The landmark SANAD study found valproate to be more effective than lamotrigine and recommended valproate as first-line treatment.[5] Furthermore, in a recently published SANAD II study, valproate was clinically more effective compared to levetiracetam in patients with generalized and unclassifiable epilepsies.[4] There were several differences in the study population of the SANAD II trial compared to our study; the median age was younger than ours (13.9 vs. 21 years), the proportion of females was almost double in our study (63.1% vs. 35%), patients were not required to have an EEG finding compatible with IGE and only 54% of the entire study group had a specific IGE epilepsy syndrome diagnosis whereas all of our patients had IGE. Currently, level C evidence supports the use of valproate, lamotrigine, topiramate and possibly also levetiracetam (level D) as initial monotherapy in generalized TCS according to the 2013 ILAE review on ASMs.[19] Moreover, valproate and topiramate are suggested to have potential efficacy in newly diagnosed JME (level D evidence).[19] Levetiracetam has also been found to be more effective than placebo in monotherapy treatment of TCS.[20] The LaLiMo trial found that lamotrigine and levetiracetam were equally effective in treating epilepsy.[21] On the contrary, lamotrigine has occasionally been found to worsen myoclonias,[22] which could limit its use in certain epilepsy syndromes.

Valproate alternatives sometimes cannot be used in the treatment of IGE in WWE. This can be due to, for instance, personal choice or a high risk of seizures as a result of switching ASM. Some women continue using valproate despite being fully aware of its adverse effects and official recommendations.[23,24] A recent study found that 68.3% of WWE continued to use valproate even after being informed of the related risks.[24] The same study found that 47% of patients wished to return to valproate after switching to alternative ASM due to the adverse effects associated with new drugs or the recurrence of seizures.[24] Switching from valproate to another ASM has been associated with worsening of seizure control but switching back to valproate has been seen to improve the patients' seizure control.[13]

In our study, the paediatric cohort achieved seizure control similar to the adult cohort. Unlike adult patients who showed a considerable change in the use of valproate, this study demonstrated that the predominant use of valproate in paediatric patients still prevailed. Valproate remains one the most prescribed medications for children in Europe,[16] in addition to ethosuximide, which is often used to treat CAE. Our results suggest that paediatric neurologists are not yet fully aware of the guidelines of valproate use in women of childbearing potential, which also include adolescents.

The present study has some limitations. This was a retrospective, uncontrolled follow-up study, and the patients were not randomized to receive any particular ASM. Furthermore, the subjects had variable clinical histories (duration of epilepsy, treatments initiated at other hospitals). Most likely, physician preference and bias played a role in drug selection and withdrawal of certain ASM treatments, but no statistical method can remove or fully account for this effect.[25] All patients were from a single centre, which limits the external validity of the findings. The patients were identified at a specialist clinic, which may lead to underrepresentation of epilepsies of more benign outcomes; on the contrary, our hospital has the responsibility of epilepsy care for a specific population. Furthermore, we were not able to state whether a drug was used as first- or second-/third-line therapy because our study population included both newly diagnosed incident cases and prevalent epilepsy cases.[26] Since these groups represent different stages of epilepsy, their prognoses may differ and lead to misleading results, possibly affecting the results in this study as well. Moreover, because the selection of use or disuse of VPA/VPA alternatives was based on the clinical judgement of the treating physician and was not done in a randomized, controlled manner, there may be a selection bias influencing the outcome comparing seizure freedom rates between VPA and VPA alternatives.

5 | CONCLUSIONS

Compared to our previous study,[15] there was a marked increase in the use of alternative ASMs to valproate due to updated treatment recommendations. The use of valproate in WWE had decreased in daily clinical practice in our centre without a higher risk of seizure recurrence. This encourages clinicians to use first-line medications other than valproate in the treatment of WWE. In general, the seizure outcome in IGE is good, and most patients can be successfully treated with monotherapy.

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CONFLICT OF INTEREST

R.K, P.B, J.R and **J.M** 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 Liva-Nova; received speaker honoraria from 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 LivaNova, Eisai, Medtronic, UCB and Pfizer. **S.R** has participated in a clinical trial for UCB.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ane.13567.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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