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ORIGINAL ARTICLE

Valproic acid use in fertile women with genetic generalized epilepsies

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Objectives: In genetic generalized epilepsies (GGE), valproic acid (VPA) is the most efficacious compound. However, due to teratogenicity and increased risk for impaired cognitive development after intrauterine exposure, its use in women of fertile age is strictly regulated but sometimes unavoidable.

Methods: All patients with GGE treated at the outpatient clinic of a tertiary epilepsy center with at least one visit between January 2015 and April 2020 were included in this retrospective study. The rate of women aged 18 to 49 years taking VPA was compared to that of men of the same age group and to women > 49 years. Furthermore, in each group, clinical variables associated with VPA use were sought.

Results: Twenty-eight out of 125 women of fertile age (22%) were treated with VPA, compared to 28 out of 56 men ≤ 49 years (50%; $p = .002$) and to 22 out of 40 female patients > 49 years (55%; $p < .001$). VPA dose was lower in fertile women compared to men, with no difference in seizure freedom rates. In women ≤ 49 years, multivariate analysis demonstrated age as the only variable independently associated with VPA use (OR 1.095; 95% CI 1.036–1.159). In the other two groups, no associated variables were identified.

Conclusions: Despite warnings with respect to teratogenicity and impaired cognitive development with VPA, from 2015 to 2020, almost every fourth women of fertile age with GGE received this compound. Inevitably lower VPA doses in these women seem sufficient for favorable seizure freedom rates.

KEYWORDS
antiseizure medication, cognitive disabilities, defined daily dose, female patients, teratogenicity

1 | INTRODUCTION

Valproic acid (VPA) is frequently prescribed among patients with genetic generalized epilepsies (GGE) and is recommended in various guidelines as antiseizure medication (ASM) of first choice for male patients with GGE, in particular in those with predominant myoclonic and tonic-clonic seizures.[1–3] These recommendations are based on the SANAD study which indicated in patients with GGE that the time to treatment failure for any reason was significantly longer for VPA than for both lamotrigine and topiramate.[4] To date, the results of an equivalent study (SANAD II) comparing the efficacy and tolerability of VPA and levetiracetam in GGE

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are still pending. Various pregnancy register studies have shown the dose-dependent teratogenic risk of VPA with rates of major congenital malformations (MCMs) of around 10% in monotherapy [5–7] and children's significantly reduced cognitive abilities across multiple domains after intrauterine exposure.[8] The favorable antiseizure efficacy and tolerability of VPA in GGE on the one hand and its potentially hazardous consequences in pregnancy on the other hand leave women of fertile age diagnosed with GGE in a therapeutic dilemma.

In October 2014 and in March 2018, the European Medicines Agency (EMA) published further strengthened measures to avoid VPA exposure during pregnancy to the extent of banning VPA treatment unless there is no other effective treatment available. Additionally, VPA must not be used in any woman or girl capable to have children unless the conditions of a strict pregnancy prevention program are met.[9,10] Various register studies have shown a declining rate of VPA use in women with epilepsy (WWE) in Europe within the last 5 to 10 years.[11–15] However, in clinical practice, a considerable number of WWE of childbearing potential and in particular those with GGE may still be treated with VPA. A recent cohort study of a single epilepsy center reported almost one in three WWE, most of which of fertile age, being treated with VPA; interestingly, a considerable number of those had focal epilepsies.[16]

The aim of the current study was to compare the rate of VPA intake in adult women with GGE of fertile age, defined as 18 to 49 years, to that in men of the same age range. Furthermore, we sought to identify, differentiated by sex, variables independently associated with VPA use. For additional comparisons, we also assessed VPA treatment in patients aged 49 years and more. Finally, we assessed doses of VPA and of concurrent ASM as well as their impact on seizure freedom rates in all groups.

2 | METHODS

2.1 | Study design and patient selection

In this retrospective study, patients treated at the adult epilepsy outpatient clinics of a tertiary epilepsy center (Charité—Universitätsmedizin Berlin, Germany) were considered, if the last consultation took place between 1st of January 2015 and 15th of April 2020. All patients aged 18 years or above who had a clear diagnosis of GGE were included into this study. GGE was diagnosed on the basis of typical seizure types and their age at onset, and, if available, of interictal EEG findings characterized by generalized 2.5–3.5/s (poly-)spike-wave complexes.

Sociodemographic, epilepsy and treatment data were retrieved from a Microsoft Access database which had been maintained by the treating physicians in clinical routine at each patient consultation.

This study is approved by the Institutional Review Board of the Charité University Hospital (EA2/181/20). Clinical information was obtained from medical records of a database only, and the need to obtain written, informed consent from each patient is waived. Data were handled under the German and the European data protection act.

The European and German pregnancy prevention programs for women with epilepsy or other neurological or psychiatric conditions treated with VPA do not define fertile age in detail but medical and legal implications demand caution. We therefore chose to apply a conservative definition based on that of the Federal Statistical Office of Germany[17] and hence determined fertile age in female patients with an upper limit value of 49 years.

2.2 | Data analysis

The following data were extracted from the database: Sex, age at onset of epilepsy, age at last consultation, GGE syndrome, seizure freedom in the 12 months prior to last consultation, number and dose of current ASM, and the Liverpool Adverse Events Profile (LAEP) score.[18] Defined daily doses (DDD) were calculated based on the ATC/DDD Index of the WHO Collaborating Centre for Drug Statistics Methodology.[19]

Statistical analysis was performed with SPSS Statistics 24.0 (IBM). Categorical variables were tested with either chi-square ($n > 50$), chi-square test with Yates correction ($n = 20–50$) or Fisher's exact test ($n < 20$). Continuous variables were tested with Kruskal-Wallis test with Dunn-Bonferroni test for post hoc analysis and Mann-Whitney U test due to skewed data distributions.

A simple linear regression model was calculated to predict proportion of patients receiving VPA based on age. Binary regression analysis (inclusion method: stepwise backward; $p < .1$ [p in], $p < .05$ [p out]; iteration 20; cutoff set at 0.5; constant included) was performed to calculate odds ratios with 95% confidence intervals as estimates for variables independently associated with VPA therapy.

Statistical significance was set at $p < .05$.

3 | RESULTS

In total, 235 patients (165 women, 70%) with GGE were included into this study, and 181 patients (125 women, 69%) were 49 years and younger. Further details on demographic and epilepsy variables are given in Table 1.

3.1 | Rate of VPA-treated patients and drug dose

Women of fertile age (28 out of 125 patients, 22%) were treated less frequently with VPA compared to men of the same age group (28 out of 56 patients, 50%; $\chi^2(1) = 13.79$, $p = .002$, V = 0.276) as well as compared to female patients aged above 49 years (22 out of 40 patients, 55%; $\chi^2(1) = 15.25$, $p < .001$, V = 0.304) (Figure 1, Table S1, Table S2).

In addition, women of fertile age received significantly lower DDD of VPA (median 0.5, corresponds to dose of 750 mg per day) compared to men of the same age (median 0.8, corresponds to dose

TABLE 1 Clinical data

	Total *n* = 235	Women ≤ 49 years *n* = 125	Men ≤ 49 years *N* = 56	Women > 49 years *n* = 40	Men > 49 years *n* = 14	*p*-value
Age at onset of epilepsy in years, median (IQR)	14 (11–17)	14 (10–17)	15 (13–18)	12 (9–17)	15 (7–19)	.404
Age at last consultation in years, median (IQR)	35 (28–48)	32 (27–39)	31 (24–38)	58 (54–69) **	62.5 (52–74)	**<.001**
Duration of epilepsy in years, median (IQR)	22 (13–34)	19 (11–25)	16 (8–22)	49 (40–56) **	48 (41–59)	**<.001**
GGE syndrome, *n* (%)						.513
Childhood absence epilepsy	25 (11%)	12 (10%)	5 (9%)	6 (15%)	2 (14%)	
Juvenile absence epilepsy	47 (20%)	26 (21%)	8 (14%)	10 (25%)	3 (21%)	
Juvenile myoclonic epilepsy	93 (40%)	50 (40%)	24 (43%)	14 (35%)	5 (36%)	
Epilepsy with GTCS alone	65 (28%)	34 (27%)	19 (34%)	9 (23%)	3 (21%)	
Unclassified GGE	5 (2%)	3 (2%)	0	1 (3%)	1 (7%)	
Terminal 12–month seizure freedom, *n* (%)	98 (42%)	55 (44%)	16 (29%)	23 (58%)	11 (79%)	**.002**
Number of current ASM, median (IQR)	1 (1–2)	1 (1–2)	1 (1–1.75)	1 (1–2)	1 (1–2)	.928
ASM monotherapy, *n* (%)	169 (72%)	90 (72%)	41 (75%)	28 (70%)	10 (71%)	.970
DDD of all ASM, median (IQR)	1.0 (0.6–1.7)	1.2 (0.7–1.8)	1.0 (0.6–2.0)	0.8 (0.5–1.3)	0.8 (0.4–1.5)	.106
VPA treatment, *n* (%)	87 (37%)	28 (22%)	28 (50%)*	22 (55%)**	9 (64%)	**<.001**
DDD of VPA, median (IQR)	0.7 (0.4–1.0)	0.5 (0.3–0.8)	0.8 (0.5–1.3)*	0.7 (0.4–1.1)	0.4 (0.4–0.9)	**.025**
LAEP-Score, median (IQR)	35 (27–43)	36 (28–44)	31 (24–40)	34 (27–41)	33 (24.5–35)	.163

Note: Given *p*-values in table reflect omnibus test for all four patient groups defined by age and sex. Significant differences in post hoc analysis between groups of interest (women ≤ 49 years vs. men ≤ 49 years and women ≤ 49 years vs. women > 49 years) are indicated by underline and * for $p < .05$ and ** for $p < .001$. See Table S1 and Table S2 for exact *p*-values of post hoc tests and further details. For terminal 12-month seizure freedom, the omnibus test for differences between groups (Kruskal-Wallis test) was significant, but post hoc analysis yielded no significant differences.

Bold indicates significant *p*-value.

Abbreviations: ASM, antiseizure medication; DDD, defined daily dose; GGE, genetic generalized epilepsies; GTCS, generalized tonic-clonic seizures; IQR, inter quartile range (25%/ 75%); LAEP, Liverpool Adverse Events Profile; n, number of patients; VPA, valproic acid.

of 1,200 mg per day; U = 201.5, Z = −2.840, $p = .027$, $r = .211$). At the same time, DDD of all current ASM did not differ significantly between women and men ≤ 49 years with VPA (median 0.8 vs. 1.0, $p = .234$). The difference in VPA DDD between women of fertile age and female patients older than 49 years (median 0.7, corresponds to dose of 1,050 mg per day) was not statistically significant after Bonferroni correction for multiple testing ($p = .241$) (Figure 1, Table S1, Table S2). In patients older than 49 years, no significant difference in prescription rate and DDD of VPA between women and men was measured (Table S3).

In post hoc analysis, no significant differences in rate of terminal 12-month seizure freedom were found between women of fertile age and men of the same age on the one hand (44% vs. 29%, $p = 1$ after multiple comparisons) and between women of fertile age and women aged above 49 years on the other hand (44% vs. 58%, $p = 1$) (Table S1, Table S2). LAEP scores were not significantly different between the three mentioned patient groups ($p = .163$; Table 1). Also, in the subgroup of patients ≤ 49 years taking VPA, the lower DDD in women ($n = 28$) compared to that in men ($n = 28$) did not impact the rate of terminal 12-month seizure freedom (50% vs. 29%, $p = .171$), and LAEP scores did also not differ significantly (median 39.0 vs. 33.5; $p = .343$).

3.2 | Parameters associated with VPA use in women of fertile age

Female patients of fertile age treated with VPA were significantly older than patients of the same group without VPA (U = 787.5, Z = −3.381, $p = .001$, $r = .302$) (Table 2). Furthermore, a simple linear regression model was calculated to predict proportion of patients receiving VPA based on age, which was significant for the group of women of fertile age ($F(1,6) = 10.150$, $p = .019$, $R^2 = .628$). For control groups (men ≤ 49 years and women > 49 years), no significant regression equation was found. The proportion of patients treated with VPA in different age groups is shown in Figure 2.

Additionally, in multivariate analysis applied for women ≤ 49 years (Table 2), age was independently associated with administration of VPA (OR 1.095, Cox & Snell R^2 .086; Nagelkerke R^2 .131, $f = 0.388$).

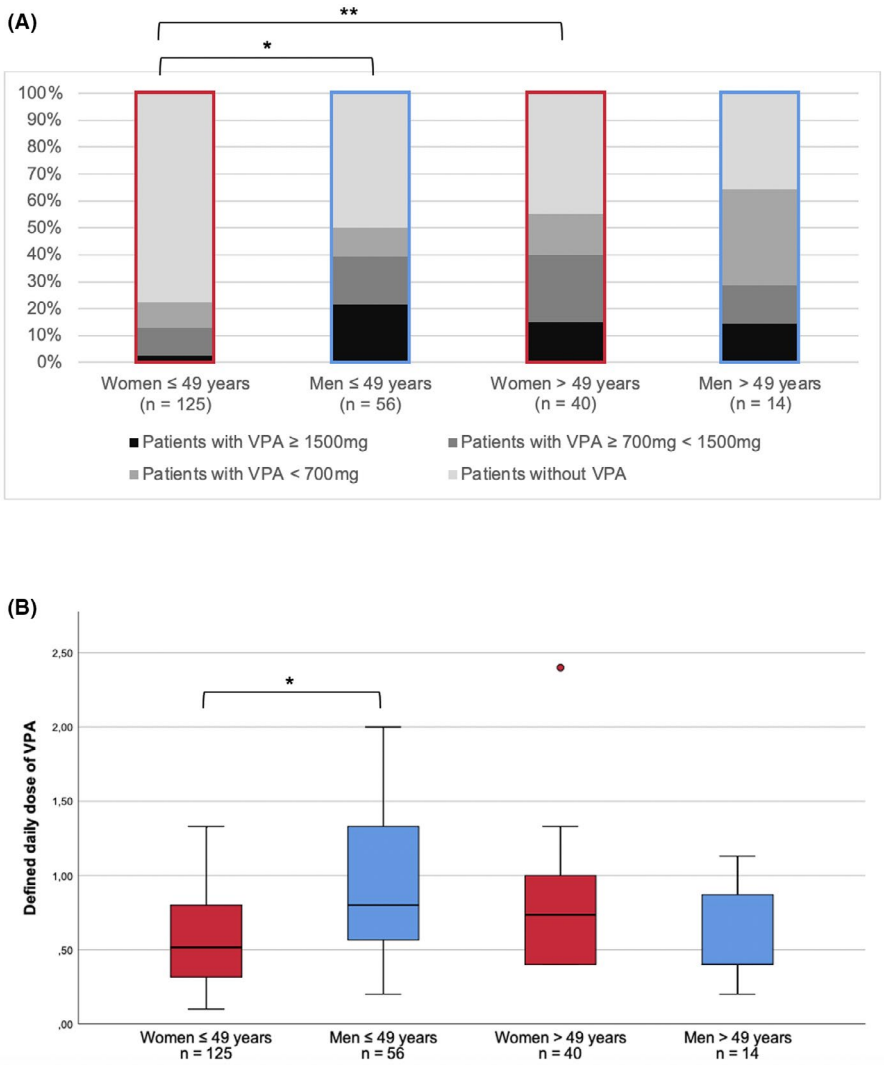


FIGURE 1 Rate of VPA treatment and VPA dose differentiated by patient groups. (A) Proportion of patients receiving valproic acid (VPA) per patient group (stratified by sex and age). For patients with VPA, dose was subdivided into three dose ranges as published previously. Level of significance is indicated for comparison of portion of VPA-treated patients between groups (*p*-values calculated with Bonferroni correction). (B) Defined daily dose of VPA per patient group, indication of significant difference after Bonferroni correction. *$p < .05$; **$p < .001$

The analysis of men in the same age group did not yield any variables associated with VPA intake, neither in univariate, nor in multivariate analysis (Table S4). Also, in the group of women > 49 years, no factors were significantly associated with VPA intake (Table S5).

Women of fertile age receiving VPA were treated with significantly lower DDD calculated over all current ASM in comparison with women of fertile age without VPA treatment (median 0.8 vs. 1.3; U = 941.0, Z = −2.480, $p = .013$, $r = .221$). Detailed information on ASM comedication can be found in Table S6. VPA dosage did not differ significantly in mono- compared to polytherapy (Table S7). The rates of terminal 12-month seizure freedom and scores of adverse events (LAEP) did not differ significantly in women of fertile age with vs. without VPA (Table 2).

3.3 | Family planning and contraception in women of fertile age receiving VPA

All WWE of fertile age were informed about pregnancy-related risks of VPA therapy and the statutory obligation to avoid VPA use on a regular basis in accordance with legal regulations. Four women mentioned the desire to have children in the near future. In three of these patients, the plan of dose reduction or discontinuation of VPA was documented. For the other patient, a reduction of VPA was waived due to former recurrent tonic-clonic seizures after dose of VPA had been reduced. Fourteen women stated clearly to have no desire to have (more) children, and for 10 women, no clear statement about a wish to have children in the medium-term was documented.

For 21 of 28 women, an effective contraception was documented, while three women were without contraception despite repeated counseling but due to individual decision with respect to their lifestyle; in four cases, information on contraception was undetermined.

In the analyzed time period, 28 out of 97 women without VPA treatment became pregnant (20 women with one pregnancy, 7 women with two pregnancies and one woman with 3 pregnancies). After comprehensive counseling, two women became intendedly pregnant while receiving VPA, as they had recurrent tonic-clonic seizures during previous therapy with levetiracetam and lamotrigine. They were treated with lowest possible VPA dosages (500 mg and 600 mg, respectively) subdivided into four takings per day and

TABLE 2 Variables associated with VPA therapy in women of fertile age

	Women with VPA *n* = 28	Women without VPA *n* = 97	*p*-value univariate analysis	OR (95% CI) in multivariate Analysis	*p*-value multivariate analysis
Age at onset of epilepsy in years, median (IQR)	14.0 (9.8–16.0)	15.0 (10.0–17.5)	.324	0.951 (0.879–1.028)	.204
Age at last consultation in years, median (IQR)	39.0 (30.0–46.0)	31.0 (25.0–37.0)	**.002**	**1.095 (1.036–1.159)**	**.001**
Duration of epilepsy in years, median (IQR)	25.0 (18.2–31.8)	18.0 (10.0–24.0)	**.001**	–	–
GGE syndrome			.185		
Juvenile and childhood absence epilepsy	8 (29%)	30 (31%)		0.864 (0.287–4.418)	.864
Juvenile myoclonic epilepsy	15 (54%)	35 (36%)		2.043 (0.615–6.783)	.243
Other	5 (18%)	32 (33%)		–	–
Number of current ASM (Median)	1	1	.335	–	–
ASM monotherapy, *n* (%)	18 (64%)	72 (74%)	.428	–	–
Defined daily dose of all ASM, median (IQR)	0.8 (0.4–1.7)	1.3 (0.7–1.9)	**.013**	–	–
Terminal 12-month seizure freedom, *n* (%)	14 (50%)	41 (42%)	.468	–	–
LAEP score (median)	39.0	35.3	.218	–	–

Note: 125 cases were included into the multivariate analysis. Cox & Snell R^2 .086; Nagelkerke R^2 .131; f = 0.388.

Bold indicates significant *p*-value.

Abbreviations: n, number of patients; IQR, inter quartile range (25%/ 75%); GGE, genetic generalized epilepsies; GTCS, generalized tonic-clonic seizures; ASM, antiseizure medication; VPA, valproic acid; LAEP, Liverpool Adverse Events Profile; OR, odds ratio; 95% CI, 95% confidence interval.

received folate preconceptionally and in the first trimenon (5 mg per day).

4 | DISCUSSION

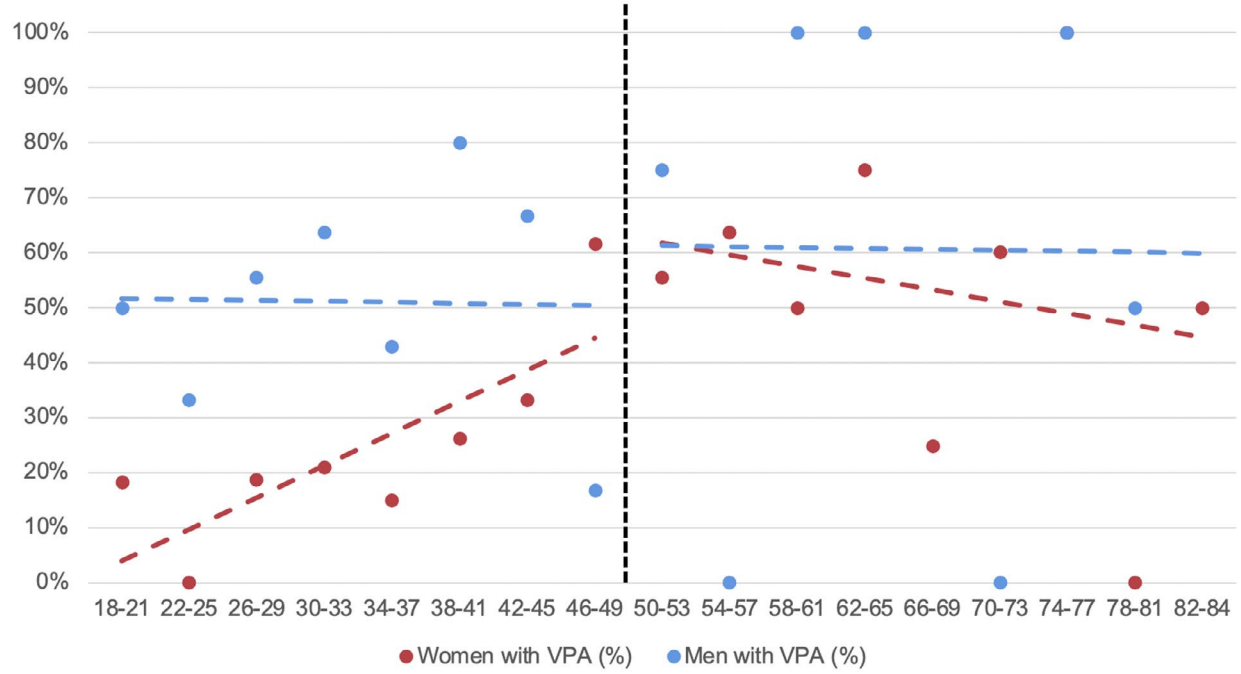
In the current large cohort of patients with GGE, we demonstrated, as expected, a significantly lower rate of VPA intake in women of fertile age compared to men of the same age and women of older age. Surprisingly, still almost one out of four women of fertile age was treated with this potentially teratogenic and for their offspring cognitively impairing compound. These risks seem to be accounted for, as women of fertile age were treated with significantly lower doses of VPA in comparison with men of the same age. Importantly, our findings demonstrate that seizure control was comparable between both groups. At the same time, defined daily doses considering all current ASM were similar between the two groups. In ASM polytherapies, the higher rate of MCMs and impaired cognitive development of the offspring is mainly driven by higher doses of VPA.[20] Thus, strikingly lower VPA doses in female patients of fertile age may be compensated by raising dose of concurrent ASM.

The lower DDD of all current ASM in women of fertile age receiving VPA compared to women of same age without VPA was not associated with a significantly lower rate of seizure freedom, confirming the high efficacy of VPA in GGE.

Based on different pregnancy registers depicting the dose-dependent risk for MCMs,[6,7,21] three dose categories of daily VPA intake (<700 mg, ≥700 mg – <1,500 mg and ≥1,500 mg) have been established.[20,21] An exponentially increasing risk of MCMs was described with rates at 5.9%, 11.0%, and 24.0%, respectively.[20] In our cohort, only three of 28 women of fertile age receiving VPA were in the highest dose group, while 13 women were treated with a moderate dose of VPA and 12 women were treated with VPA in the lowest dose category (Figure 1). Both women who became pregnant while receiving VPA were treated with lowest possible dose <700 mg per day.

In comparison with recently published data of a cohort of consecutive female patients with epilepsy in Poland, most of which were of fertile age, the proportion of women with GGE treated with VPA (47 of 98 women, 48%)[16] was more than twice as high as in the current study (28 of 125 women, 22%). The high rate in the former study may be explained by the reported high proportion of patients who rejected withdrawal of VPA. This is notably astonishing, as half of the patients had focal epilepsies and no need for VPA use, due to a plethora of more favorable alternatives.

In the current study, VPA treatment was independently associated with a higher age in fertile women. The likelihood of being treated with VPA increased statistically by around 10% per year of age, in particular with an augmentation in the age group between 38 and 49 years. This finding may reflect the physician's anticipation of a decreasing probability of pregnancies by higher ages in



Age (years)	18-21	22-25	26-29	30-33	34-37	38-41	42-45	46-49	50-53	54-57	58-61	62-65	66-69	70-73	74-77	78-81	82-84
Women total (n)	11	16	16	24	20	19	6	13	9	11	2	4	4	5	1	2	2
Women with VPA (%)	18	0	19	21	15	26	33	62	56	64	50	75	25	60	100	0	50
Men total (n)	6	9	9	11	7	5	3	6	4	2	1	2	0	1	2	2	0
Men with VPA (%)	50	33	56	64	43	80	67	17	75	0	100	100		0	100	50	

FIGURE 2 Proportion of patients receiving VPA by age groups and sex. Percentage of patients per 4-year age groups receiving valproic acid (VPA) in mono- or polytherapy, differentiated by sex. Linear trends are indicated separately for each patient group by dashed lines. Test statistics of simple linear regression analysis: Women ≤ 49 years (fertile age): y = 0.058x–0.018; R^2 = .633; p = .019. Men ≤ 49 years: y = −0.002x + 0.518; R^2 = 0.0004; p = .973. Women > 49 years: y = −0.021x + 0.810; R^2 = .042; p = .587. Men > 49 years: y = −0.002x + 0.628; R^2 < .001; p = .983

the course of completion of family planning. A further likely covariate of VPA treatment in higher ages is the increasing probability of treatment failure with other antiepileptic drugs over time. The result of an age-dependent increase of VPA prescription is in line with data of a comprehensive analysis of health insurance providers in Germany with around 3.5 million subjects. For 2015, the study reported, independently of treatment indication, an at least 1.5 times higher portion of VPA use in women aged between 41 and 50 years compared to females between 12 and 35 years of age.[15]

In clinical practice as well as in this study, definition of fertile age plays a crucial role. In 2016, mean age of women giving birth in Germany was 31.3 years (SD 5.2).[22] Accounting a normal distribution of age, around 95% of women at birth were between 20.9 and 41.8 years old. As we considered the effect of the official warning of the European Medicines Agency,[9,10] which does not define fertile age into detail, a rather cautious definition of fertile age needed to be applied. Eventually, we chose the definition of the Federal Statistical Office of Germany determining fertile age with an upper limit value of 49 years.[17]

One limitation of this study is the selection of patients. Data were derived from a specialized epilepsy outpatient clinic; thus, the rate of patients with difficult-to-treat GGEs might be higher, which may result in an over-representation of women of fertile age receiving VPA. Accounting 22% of female patients treated with VPA, the rate in the current cohort is slightly higher compared to the analysis of health insurance providers in Germany mentioned above, which noted for 2015 a rate of VPA treatment of 16.8% in girls and women with epilepsy aged between 12 and 50 years.[15] The cross-sectional design of the current study also displays WWE of fertile age at different stages of treatment optimization in a tertiary epilepsy center. Therefore, in some cases, weaning VPA for alternative ASM is still an option.

This selection bias is also the most likely explanation for the relative over-representation of women of fertile age in the current cohort compared to men of the same age group. At the same time, women of fertile age constituted the focus of this study with a sufficient number of patients for adequate statistical analysis.

Due to the monocentric design, generalizability of our data may not be feasible.

Further, reliable data on status of family planning and folate intake were limited, owing to the retrospective study design. Nonetheless, data on family planning of the current study are comparable to results of the cohort study of a Polish epilepsy center mentioned above.[16] Also due to the retrospective cross-sectional design, comprehensive data on ASM treatment prior to administration of VPA were not available for every patient. Valid data on body weight and ASM serum levels could not be referred to as these were not obtained in a standardized manner at defined time points during clinical routine. On the other hand, the retrospective approach constitutes an advantage as we were able to analyze "real life data" without treatment bias.

5 | CONCLUSION

Despite strict regulations due to teratogenic risks and possible impairment of children's cognitive development, in an academic epilepsy outpatient clinic, almost one out of four women of fertile age with GGE received VPA. In this group, higher age was independently associated with VPA use.

The significantly lower VPA doses in women of fertile age in comparison with men of same age did not result in reduced rates of seizure freedom, as other ASM were compensatorily administered. Thus, if use of VPA in women of fertile age with GGE is unavoidable, strikingly lower doses are of paramount importance to reduce the risk of teratogenicity but do not seem to come at the expense of reduced efficacy.

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CONFLICT OF INTEREST

MH received speaker's honoraria and/or consultancy fees from Arvelle, Bial, Desitin, Eisai, GW Pharma, UCB, and Zogenix within the last 3 years. The other authors have declared that no competing interests exist.

AUTHOR CONTRIBUTIONS

D.S. involved in acquisition of data, interpretation and analysis of data, and writing the manuscript. V.G. and M.H. involved in design of the study, interpretation of data, and revising the manuscript. A.K. involved in design of the study and acquisition of data.

ETHICAL APPROVAL

This study is approved by the Institutional Review Board of the Charité University Hospital (EA2/181/20) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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