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RESEARCH ARTICLE

Valproate discontinuation in girls and women of childbearing age with epilepsy: An Italian multicenter retrospective study on prescribing patterns and outcomes

Roberta Esposto[1] | **Giovanni Falcicchio**[2] | **Elena Zambrelli**[3] | **Emanuele Cerulli Irelli**[4] | **Giulia Monti**[5] | **Federica Ranzato**[6] | **Loretta Giuliano**[7] | **Angela La Neve**[2] | **Carlo Adrea Galimberti**[8] | **Laura Maria Beatrice Belotti**[9] | **Katherine Turner**[3] | **Cecilia Catania**[4] | **Diana Polo**[6] | **Valeria Todaro**[7] | **Francesca Bisulli**[1,10] | **Barbara Mostacci**[1] | **Appendix A: Epilepsy and Gender Commission of the LICE (Italian chapter of the ILAE)**

[1]IRCCS Institute of Neurological Sciences of Bologna, Full Member of the European Reference Network EpiCARE, Bologna, Italy

[2]Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Bari, Italy

[3]Epilepsy Center, Sleep Medicine Center, Childhood and Adolescence Neuropsychiatry Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, Milan, Italy

[4]Department of Human Neurosciences, Sapienza University, Rome, Italy

[5]Neurology Unit, Ospedale Ramazzini di Carpi, AUSL di Modena, Carpi, Italy

[6]Epilepsy Center, Neurology Unit, Vicenza, Italy

[7]Department of Medical, Surgical Sciences and Advanced Technologies G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy

[8]Epilepsy Center, Mondino Foundation, IRCCS, Pavia, Italy

[9]Epidemiology and Statistics Unit, IRCCS, Istituto Delle Scienze Neurologiche Di Bologna, Bologna, Italy

[10]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

Correspondence
Roberta Esposto, IRCCS Institute of Neurological Sciences of Bologna, Full Member of the European Reference Network EpiCARE, Via Altura 3, Bologna 40139, Italy.
Email: robertaesposto.93.re@gmail.com

Abstract

Objective: This study aimed to identify prescribing behaviors in women of childbearing potential (WOCP) with epilepsy already taking valproate (VPA), and to investigate the relationship between VPA maintenance, substitution, reduction, or withdrawal as part of polytherapy, and seizure worsening or relapse.

Methods: We retrospectively reviewed the prescription behaviors and seizure outcomes in WOCP (16–50 years of age) with epilepsy, referred to eight Italian epilepsy centers, who were taking VPA for at least 1 year between 2014 and 2019.

Results: Among 750 women (~12% of all WOCP), 528 (70.4%) maintained VPA unchanged throughout the observation period, 103 (13.7%) replaced VPA with another antiseizure medication (ASM), 90 (12%) reduced VPA, and 29 (3.9%) discontinued VPA in polytherapy. Focal epilepsy was most strongly associated with VPA withdrawal (odds ratio [OR] 2.96, 95% confidence interval [CI] 1.38–6.38),

whereas generalized epilepsy was most associated with its non-withdrawal (reduction/switch/maintenance) (OR .31, 95% CI .14–.68). Intellectual disability, higher seizure frequency, and higher VPA doses were linked to VPA continuation. VPA withdrawal from polytherapy was associated with a higher risk of tonic–clonic seizure worsening (OR 2.91, 95% CI 1.09–7.77) compared to non-withdrawal.

Significance: VPA was rarely withdrawn or substituted in WOCP with epilepsy, in secondary and tertiary care settings following European regulatory restrictions. This likely reflects a population with severe epilepsies where VPA is difficult to replace; whereas women with milder epilepsies likely discontinued VPA earlier, as evidenced by its low overall prescription frequency. Withdrawal of VPA from a polytherapy regimen was associated with a threefold increased risk of seizure exacerbation.

KEYWORDS

focal epilepsy, generalized epilepsy, tonic-clonic seizures

1 | INTRODUCTION

Valproate (VPA) is acknowledged as a first-line therapy for generalized tonic–clonic seizures (GTCSs), absence seizures, and myoclonic seizures. Its efficacy has been largely demonstrated, even in comparison with other treatments,[1,2] thus is traditionally considered the preferred treatment for idiopathic generalized epilepsies (IGEs).[3–5]

In addition, VPA demonstrates effectiveness against tonic seizures, atonic seizures, and epileptic spasms, thus justifying its use in epileptic encephalopathies such as Dravet syndrome, especially if aggravated by sodium channel–blocking antiseizure medications (ASMs).[1,4]

In focal epilepsies, VPA is not typically considered a preferred first-line treatment[3] due to concerns about tolerability and the availability of several alternative ASMs; however, it remains an important option in polytherapy for drug-resistant epilepsies.[2]

Regrettably, intrauterine exposure to VPA is associated with a two- to sevenfold dose-dependent increased risk of major congenital anomalies (MCAs), compared to other commonly used ASMs, with an average prevalence of 10%.[6–8] Furthermore, prenatal exposure to VPA has been linked to heightened risk of neurodevelopmental delay (ND),[9–13] autism spectrum disorder (ASD),[14,15] and attention-deficit/hyperactivity disorder (ADHD).[11,12,16]

In response to this evidence, European drug regulatory authorities have issued recommendations since 2014,[17] updated in 2018,[18] advising against prescribing VPA to girls and women of childbearing potential (WOCP) unless other treatments are ineffective or intolerable and highly effective contraceptive measures are used. However, implementing these restrictions can present ethical challenges in certain complex clinical scenarios,[19] where denying VPA therapy to female patients may result in less-effective treatment compared to their male counterparts. Notably, various authors, including an International League Against Epilepsy (ILAE) Task Force,[20] have highlighted situations where VPA remains a suitable option for girls and women with epilepsy (WWE). This is particularly the case for epilepsies with a high likehood of resolution before puberty or severe epilepsies associated with significant developmental disabilities where future pregnancy is highly improbable. Moreover, if using VPA as a first choice is currently considered unacceptable in girls and WOCP with epilepsy, altering an already established therapy with VPA poses additional challenges for the clinician.

Key points

- European authorities restricted valproate (VPA) use in women of childbearing potential (WOCP) in 2014 and 2018 due to risks to offspring.
- The study analyzed the prescribing behaviors of epileptologists and their consequences in WOCP already using VPA during 2014–2019.
- VPA overall prescriptions were low, but most WOCP already taking VPA continued use.
- VPA continuation was linked to intellectual disability, frequent seizures, and high doses; focal epilepsy was linked to VPA discontinuation.
- Stopping VPA in polytherapy almost tripled the risk of tonic–clonic seizures.

Given the complexity of this issue, this study aims to analyze the prescribing behaviors of epileptologists regarding VPA management in WOCP, who are already using it as part of their antiseizure therapy. In addition, it seeks to investigate the relationship between VPA maintenance, withdrawal in polytherapy, substitution, or reduction, as well as the course of seizures. The ultimate goal is to contribute insights that will optimize treatment strategies for addressing the challenges of VPA use in WWE.

2 | MATERIALS AND METHODS

2.1 | Patient selection and definition of cohorts

Eight Italian second- and third-level epilepsy clinics participated in this study. We retrospectively reviewed the medical records of all girls and women with a diagnosis of epilepsy, age16–50 years at first observation, who had used VPA for at least 1 year during 2014–2019 and had a follow-up of at least 1 year. Women who discontinued VPA in a monotherapy regimen (complete ASM withdrawal) were excluded, as this implies that epilepsy was considered probably resolved or that the diagnosis of epilepsy was excluded. Women with incomplete clinical documentation were also excluded. Clinical data were retrospectively extracted from medical records, whereas electroencephalography (EEG) findings were obtained from written reports prepared by experienced electroencephalographers. Data collection involved contributions from eight epileptologists across the eight participating centers.

The local ethics committees approved the retrospective study protocol.

2.2 | Clinical and EEG data collection, definitions

We classified the population into four cohorts:

1. Women who continued VPA at an unchanged dose throughout the observation period.
2. Women for whom a VPA dose reduction was made.
3. Women who switched from VPA to another ASM.
4. Women receiving polytherapy from whom VPA had been withdrawn.

During the period 2014–2019, the following time points were considered:

T0: for women in Group 1, the first observation in the reporting period; for the others, the time at which therapy was changed.

T1: 1 year (±3 months) apart from T0.

The following data were collected from the medical records at T0.

1. Demographic and clinical data: Age, referral epilepsy center, schooling, age at onset of epilepsy, age at diagnosis, type of epilepsy according to the ILAE criteria,[21] seizure type (GTCSs, myoclonic, absence, focal, focal to bilateral tonic–clonic [FBTCSs], tonic, atonic, spasms), seizure frequency (multi-daily/daily, multi-weekly, weekly, multi-monthly, monthly, multi-annual, sporadic, seizure freedom >12 months), months of seizure freedom at T0, and maximum period of seizure freedom.

2. Data on intellectual disability (ID) and psychiatric comorbidities: ID was calculated on the basis of intelligence quotient (IQ), with non-testable patients categorized as having "severe" intellectual disability; all psychiatric disorders were included, and the use of psychiatric medications prescribed for other conditions was also considered as a proxy for psychiatric disorders.

3.Treatment-related data: Current ASMs; VPA regimen, blood levels where available; maximum prescribed dose of VPA; previously tried ASMs; previous failed ASMs; and previous attempts to switch, discontinue, or reduce VPA.

4. EEG characteristics: Presence of focal or generalized epileptiform discharges (EDs), photosensitivity (recorded with scalp electrodes placed according to the International 10–20 system with bipolar and reference montages).

5. Reproductive history: in particular, regarding pregnancy wish/planning the investigators were instructed to check the medical records for any documented pregnancy wish/planning, which is assessed routinely at the involved centers and recorded. Nevertheless, because the desire for pregnancy is not always clearly stated by patients, it is possible that some data may have been omitted.

At T1 (i.e., 1 year after T0), the following data were reevaluated: frequency of tonic–clonic seizures (TCSs)/non-TCSs, EEG characteristics, and adverse effects.

We assessed the frequency of seizures considering three macro-categories: TCSs, non-TCSs with fall, and other seizures (i.e., seizures that did not meet the criteria for the two other categories).

Seizure outcome was defined as the worsening of seizures (moving from a lower to a higher seizure frequency class, considering any type of seizure) or seizure recurrence in previously seizure-free (at least 12 months) women (Appendix A).

2.3 | Statistical analysis

For descriptive statistics, categorical variables were summarized with absolute (n°) and relative (%) frequencies,

and continuous variables with mean and standard deviation (SD) or median and interquartile range (IQR), based on the distribution. Normality of continuous variables distribution was checked using the Skewness–Kurtosis test. To examine the associations between categorical variables, the chi-square test was used, and in the case of low expected frequencies, the Fisher exact test was used, whereas to analyze the association between a quantitative and a qualitative variable, the Mann–Whitney *U* test was used or in the case of multiple categories, a Kruskal–Wallis test was used.

Univariate logistic regression models were used to examine the association between outcome (worsening of seizure control or relapse in previously seizure-free patients) and exposure (the four previously defined groups of women). In addition, individual factors associated with outcome or exposure were analyzed.

A multivariate logistic regression model was implemented to evaluate the association between exposure and outcome, adjusted for confounding factors. Confounding factors were defined on the basis of both clinical knowledge and their univariate-level association with outcome and exposure. The confounders used in the multivariate model were as follows: IGE, generalized EDs on the EEG, photosensitivity, TCSs, seizure frequency, previous attempt to replace VPA, and daily dose of VPA.

Statistical analyses were performed using STATA SE (version 16.1).

3 | RESULTS

We reviewed data from 750 WOCP, mean age ± SD of 29.7 ± 11 years. Demographic and general data are detailed in Table 1.

TABLE 1 Demographic and general data.

	Frequency	Percentage
Year of study entry		
2014	276	38.3%
2015	129	17.9%
2016	64	8.9%
2017	64	8.9%
2018	124	17.2%
2019	63	8.7%
Total	720	100.0%
Missing	30	
	Frequency	**Average**
Age	750	29.7 ± 11
Age at onset	697 (missing 53)	11 ± 8
Age at diagnosis	686 (missing 64)	11.7 ± 8.3
	Frequency	**Percentage**
Education		
Primary school diploma	18	4.5%
Secondary school diploma	97	24.5%
High school diploma	187	47.2%
University degree	59	14.9%
University student	35	8.8%
Total	396	100.0%
Missing	354	
Intellectual disability (ID)		
No ID	487	65.1%
Mild ID	71	9.5%
Moderate ID	121	16.2%
Severe ID	69	9.2%
Total	748	100.0%
Missing	2	
Psychiatric comorbity		
No	554	74.7%
Yes	188	25.3%
Total	742	100.0%
Missing	8	

3.1 | Epilepsy and EEG characteristics

Generalized epilepsy was the predominant type (61.5%, $n = 461$), followed by focal epilepsy (36.6%, $n = 274$); the remaining 14.5% ($n = 108$) was classified as "undefined/unknown."

Regarding the etiology, 301 (41.2%) were classified as IGE, 120 (16.4%) as structural, 77 (10.5%) as genetic, 3 (.4%) as infectious, 50 (6.8%) as "other," and 180 (24.6) as unknown.

A total of 422 women (40.4%) had GTCSs; 40.2% ($n = 289$) had FBTCSs, 39.2% ($n = 293$) focal seizures (all types), 33.6% ($n = 251$) absences, 32.3% ($n = 242$) generalized myoclonic seizures, 6.1% ($n = 44$) tonic seizures, 6.1% ($n = 43$) atonic seizures, and 2.3% ($n = 20$) had spasms.

At baseline evaluation (T0), most women were either seizure-free for 12 months or had sporadic seizures of any type. A smaller percentage experienced multi-monthly, weekly or multi-weekly, or daily or multi-daily seizures. The frequency of each seizure type is summarized in Table 2.

The median period of seizure freedom, expressed in months, was 12 (IQR 0–70).

TABLE 2 Frequency of any seizure type.

Tonic–clonic seizures frequency	Frequency	Percentage
SF > 12 months	401	54.8%
Sporadic	220	29.6%
Multi-annual	48	6.5%
Monthly	15	2.0%
Multi-monthly	25	3.4%
Multi-weekly	17	2.29%
Daily/multi-daily	10	1.35%
Total	742	
Non tonic–clonic seizures with fall frequency	**Frequency**	**Percentage**
SF > 12 months	579	85.9%
Sporadic	34	5.0%
Multi-annual	10	1.5%
Monthly	6	0.9%
Multi-monthly	17	2.5%
Multi-weekly	14	2.0%
Daily/multi-daily	14	2.0%
Total	674	
Other seizures	**Frequency**	**Percentage**
SF > 12 months	301	42.2%
Sporadic	155	21.2%
Multi-annual	59	8.0%
Monthly	36	5.0%
Multi-monthly	60	8.2%
Multi-weekly	47	6.4%
Daily/multi-daily	63	8.6%
Total	729	

Abbreviation: SF, seizure freedom.

At T0 we collected EEG data for 663 women: 234 (35.3%) had no EDs, 192 (29%) had generalized EDs, and 237 (35.8%) had focal EDs. Regarding photosensitivity, we had data on 681 women: 117 (17.18%) had a photoparoxysmal response.

3.2 | Treatment

At baseline evaluation, the mean (± SD) daily dose of VPA was 883.5 (± 425.5) mg/day and the median year of initiation of VPA therapy was 2006 (IQR 1999–2012). The maximum mean dose of VPA taken by the women in their medical history was 1018.04 ± 842 mg/day. The mean measured blood level was 63.9 ± 24.5 μg/mL (median 63 μg/mL; IQR 47.0–80.7). Of the total number of subjects, 379 (52.5%) were receiving polytherapy. The most prescribed ASM in addition to VPA was lamotrigine (LTG; 135/379), followed by levetiracetam (LEV; 96/379), clobazam (CLB; 59/379), carbamazepine (CBZ; 55/379), topiramate (TPM; 43/379), clonazepam (CNZ; 25/379), lacosamide (LAC; 27/379), zonisamide (ZNS; 23/379), oxcarbazepine (OXC; 10/379), perampanel (9/379), ethosuximide (17/379), and other ASMs in 163 of 379 (including phenobarbital, rufinamide, primidone, gabapentin, vigabatrin, tiagabine, and cannabidiol). Eighty-six women (55%) never underwent VPA substitution or discontinuation prior to 2014, although for 51of 750 this information could not be traced.

3.3 | Reproductive history

Given the retrospective nature of the study, it was not always possible to obtain all the details of reproductive history. Specifically, "pregnancy willingness or planning" was available for 671 WOCP (79 missing).

Based on the available data of 671 WOCP, 152 (22.6%) declared a willingness or planning to be pregnant at T0, whereas 519 (77.4%) did not. In addition, 130 had had previous pregnancies, and 15 were pregnant at the time of the first observation.

We have limited data on the health status of the children born to the enrolled women. Among 342 children, 8 had ascertained MCAs and/or ND; however, this was not systematically reported.

3.4 | General data

In 528 women (70.4%), VPA was maintained at an unchanged dose; in 103 (13.7%), the dose was reduced; in 90 (12%), VPA was replaced with another ASM; and in 29 (3.9%), VPA was withdrawn from a polytherapy regimen.

We determined the percentage of women 16–50 years of age who received VPA among those with epilepsy in the same age group followed at participating centers during the 2014–2019 period. This calculation was performed for all centers except one, which had recruited 63 women. The results showed that 12% of WOCP managed at the remaining seven centers were treated with VPA.

3.5 | Prescribing behaviors and their determinants

We first analyzed individual factors associated with the continuation of VPA (maintenance at an unchanged dose) vs its modification (withdrawal, switching, or dose

reduction), using logistic univariate analyses. Figure 1 summarizes the significant findings.

The factors most strongly associated with VPA modification were pregnancy wish/planning and the number of seizure-free months. Notably, the median number of seizure-free months was higher in girls or women whose VPA was modified (24 months vs 12 months). In addition, the absence of epileptiform activity (EA) on EEG was a significant factor.

Conversely, factors associated with the continuation of VPA included ID and TCS frequency. Specifically, as the frequency class increased by one level, the probability of modifying therapy decreased by nearly 30%. The daily dose of VPA was also relevant: women who continued VPA had a median dose of 900 mg/day, compared to 800 mg/day in women whose therapy was altered. We observed that for every 100 mg/day increase in VPA, the probability of changing therapy decreased by 4%.

Next, we analyzed individual factors associated with VPA withdrawal compared to its maintenance or switching to another ASM. Table 3 presents the clinical and electrophysiological data comparing women who discontinued VPA with women who did not. Table 4 summarizes the determinants of VPA withdrawal vs continuation. Notably, regarding the daily dose of VPA, we observed a gradient: for every 100 mg/day increase in VPA, the probability of discontinuation decreased by 20%.

3.6 | Seizure outcome at T1 and factors associated with worsening

In univariate analyses, we observed that women who modified VPA therapy (through reduction, switching, or withdrawal) did not experience a significantly increased risk of seizure worsening or relapse compared to those who continued VPA at the same dose. However, when comparing VPA withdrawal within a polytherapy regimen to other management strategies (maintenance at an unchanged or reduced dose or switching to another ASM), our analysis revealed a higher risk of seizure worsening (odds ratio [OR] 2.85, 95% confidence interval [CI] 1.21–6.72; $p = .016$). Specifically, when considering only the frequency of TCSs, both generalized and focal-to-bilateral, this risk increased nearly fivefold (OR 4.70, 95% CI 1.67–13.30; $p = .001$). Multivariate statistical analysis confirmed that discontinuation of VPA in a polytherapy context was associated with a nearly threefold increased risk of TCS worsening (OR 2.91, 95% CI 1.09–7.77) compared to other strategies. No significant association was found regarding seizure relapse.

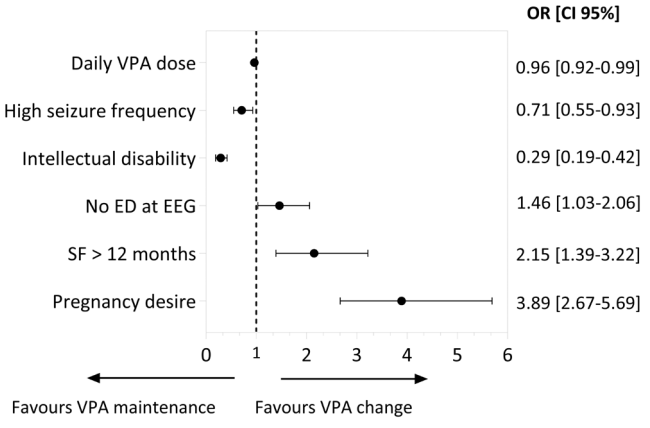

FIGURE 1 Factors associated with change/continuation of VPA therapy. Abbreviations: EEG, electroencephalography, EDs, epileptiform discharges; VPA, valproate; OR: odds ratio; CI, confidence interval.

We were unable to identify factors associated with seizure worsening within the three cohorts that modified VPA therapy, as women for whom VPA was either reduced or substituted did not exhibit worsening seizures, and the small number of women who discontinued VPA was insufficient for robust factor identification. Nevertheless, we performed an analysis to investigate factors associated with seizure worsening across the entire study population. The logistic univariate analysis showed that factors associated with seizure worsening were: focal EDs on EEG (OR 2.32, 95% CI 1.31–4.10; $p = .004$), polytherapy (OR 2.07, 95% CI 1.31–3.27; $p = .002$), focal seizures (OR 1.85, 95% CI 1.19–2.87; $p = .006$), focal epilepsy (OR 1.66, 95% CI 1.07–2.58; $p = .023$), high seizure frequency (> weekly) at T0 (OR 1.20, 95% CI 1.06–1.36; $p = .004$), seizure freedom (especially <12 months: OR 1.68, 95% CI .18–.59; $p < .001$), and higher daily dose of VPA: 1000 mg/day vs 800 mg/day ($p = .002$). Again, there was a gradient: for every 100 mg of VPA per day, the odds of worsening increased by 6% ($p = .013$).

Among the 103 women who substituted VPA with another ASM, data on the chosen medication were missing for 5 cases. Of the remaining 98 women, 90 switched to a single alternative drug, whereas 8 transitioned to polytherapy ($n = 4$ with LTG + CNZ; $n = 3$ with LTG + LEV; $n = 1$ with LAC + ZNS). The most frequently selected ASM was LEV ($n = 56$). Figure 2 illustrates the ASMs used to replace VPA as monotherapy. We found no significant difference in seizure worsening between those who switched to monotherapy vs polytherapy.

4 | DISCUSSION

In our study we evaluated, in WOCP 16–50 years of age taking VPA, the prescribing patterns and seizure outcomes across four different treatment strategies:

TABLE 3 Comparison of clinical, electrophysiological, and imaging findings in women who discontinued VPA vs those who did not.

	VPA withdrawal ($n = 29$)	VPA non-withdrawal ($n = 721$)	p
Generalized epilepsy, *n* (%)	10 (34.5)	451 (62.7)	.004
Focal epilepsy, *n* (%)	18 (62.1)	256 (35.6)	.005
Undefined epilepsy, *n* (%)	2 (6.9)	106 (14.8)	ns
IGE, *n* (%)	8 (27.5)	293 (41.7)	ns
Structural etiology, *n* (%)	9 (31)	111 (15.8)	ns
Unknown etiology, *n* (%)	8 (27.6)	172 (24.5)	ns
Genetic etiology, *n* (%)	1 (3.4)	76 (10.8)	ns
Generalized EDs, *n* (%)	3 (1.3)	234 (98.7)	.041
Focal EDs, *n* (%)	13 (6.8)	179 (93.2)	ns
No EDs, *n* (%)	11 (4.7)	223 (95.3)	ns
FBTCs, *n* (%)	4 (14.8)	285 (41.2)	.001
GTCSs, *n* (%)	15 (51.7)	434 (60.3)	ns
Absences, *n* (%)	8 (29.6)	243 (33.8)	ns
Myoclonic seizures, *n* (%)	6 (21.4)	236 (32.8)	ns
Focal seizures, *n* (%)	18 (64.3)	275 (38.3)	.008
Tonic seizures, *n* (%)	1 (4.2)	42 (6.7)	ns
Atonic seizures, *n* (%)	2 (7.4)	42 (6.1)	ns
Spasms, *n* (%)	0 (0)	20 (3.2)	ns
Intellectual disability, *n* (%)	6 (20.7)	255 (35.5)	ns
Psychiatric comorbidity, *n* (%)	7 (25)	181 (25.4)	ns
Pregnancy wish/planning, *n* (%)	8 (24.6)	144 (22.4)	ns
Median months of SF, months (IQR)	24 (9–48)	12 (0–72)	ns
Median VPA daily dose, mg (IQR)	600 (400–900)	800 (600–1000)	.001
Median VPA plasmatic level, ug/mL (IQR)	63 (47–81)	42 (26–71)	ns
Polytherapy, *n* (%)	29 (100)	530 (50.5)	ns
Previous VPA suspension attempt, *n* (%)	1 (3.9)	93 (13.8)	ns

Abbreviations: EDs, epileptiform discharges; EEG, electroencephalography, FBTCs, focal to bilateral tonic–clonic seizures; GTCSs, generalized tonic–clonic seizures; IGE, idiopathic generalized epilepsy; IQR, interquartile range; ns, not significant; SF, seizure freedom; VPA, valproate.

maintenance, reduction, substitution, and withdrawal within a polytherapy context.

We found that a very small proportion (3.9%) of WOCP in eight Italian epilepsy centers discontinued VPA, with most (70.4%) maintaining their prescribed dose. This likely reflects the period studied (2014–2019): it was demonstrated that there was a strong tendency among Italian epileptologists not to prescribe VPA to girls and WOCP even before regulatory warnings.[19] A similar trend was observed in Sweden, where the number of WWE in whom treatment with VPA was initiated had declined before the European Medicines Agency (EMA) 2014 warning and remained stable thereafter.[22] It is possible that women with milder epilepsies had already switched from VPA, leaving only those for whom alternative treatment was not feasible due to seizure control concerns. Moreover, this study was conducted in second- and third-level centers, where the most complicated cases are referred.

In these severe forms of epilepsy, where VPA is frequently the medication that has achieved seizure control, withdrawal or even substitution represents a particularly delicate intervention, and therefore the patients' distrust of withdrawal must also be taken into account, all followed at the partecipating . This finding is further supported by the fact that women aged 16 to 50 who were exposed to VPA during the five-year period accounted for 12% of all women in the same age group followed at the participating centers.

We found that two main factors influence the decision to modify VPA therapy. The first was pregnancy willingness or planning, indicating an attempt to secure a pregnancy without VPA, and reflecting the awareness of the EMA restrictions and the teratogenic effects of VPA. The second was good epilepsy control (absence/low frequency of TCSs, seizure freedom for 12 months or more, absence of EDs, median daily dose of VPA less than 800 mg). This

TABLE 4 Factors associated with VPA withdrawal and non-withdrawal.

	OR	CI	*p*
Factors associated with VPA withdrawal			
Focal epilepsy	2.96	1.38–6.38	.005
Focal seizures	2.89	1.32–6.37	.008
Factors associated with VPA non-withdrawal			
Generalized epilepsy	0.31	0.14–0.68	.004
Generalized Eds	0.26	0.07–0.94	.041
FBTCSs	0.25	0.085–0.72	.011
Daily VPA dose	0.998	0.996–0.999	.001

Abbreviations: CI, confidence interval; EDs, epileptiform discharges; FBTCSs, focal to bilateral tonic–clonic seizures, VPA, valproate.

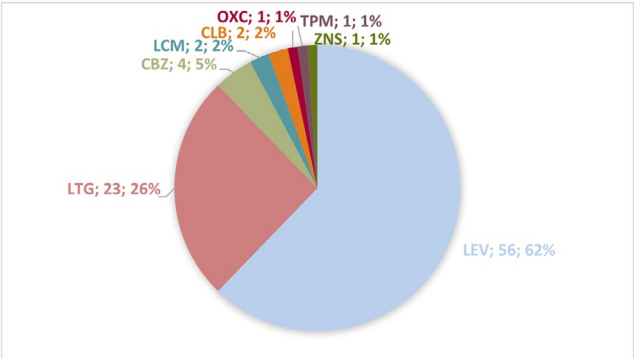

FIGURE 2 VPA replacing monotherapy.
Abbreviations: CBZ, carbamazepine; CLB, clobazam; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; TPM, topiramate; ZNS, zonisamide.

likely reflects the desire to make the withdrawal as safe as possible for WWE without exposing them to an increased risk of seizure recurrence. Regarding pregnancy as a determinant factor for VPA therapy modification, this is consistent with Cerulli Irelli et al.,[23] who investigated the relationship between VPA avoidance/switching and seizure outcome in WOCP with IGE, and also with Atalar et al.,[24] who found that one of the main predictors of continuing VPA in WWE was the lack of pregnancy expectancy. Another most recent multicenter study that has investigated the predictors of seizure recurrence in WOCP with IGE who switched from VPA to alternative ASMs showed that the most common reason for VPA switch was teratogenicity concern.[20]

Atalar et al.[24] found that the main determinants of continuing VPA therapy, in addition to pregnancy desire, were fear of seizure recurrence and significant cognitive impairment. In their study, the association with seizure type, EEG characteristics, average daily dose of VPA, and months of seizure freedom at follow-up was not statistically significant.

When specifically examining the cohort that withdrew from VPA, focal epilepsy and, consistently, the presence of focal seizures were the factors most strongly associated with withdrawal. Symmetrically, generalized epilepsy and the presence of generalized EDs deterred the withdrawal of VPA, probably due to the awareness that these conditions are more prone to exacerbation after discontinuing this medication. A study utilizing data from the Australian Register of Antiepileptic Drugs in Pregnancy indicated that women who ceased VPA before pregnancy faced an increased risk of seizures during pregnancy, especially in cases of IGE.[25] Similarly, data from the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) showed that women who withdrew from VPA or switched to another ASM during the first trimester had a higher likelihood of experiencing GTCSs during pregnancy, compared with those who continued VPA throughout the first trimester.[22] An Italian multicenter study reported that 20 of 28 women with IGE who discontinued VPA due to planned pregnancies experienced a seizure worsening, mostly within the first 3 months.[23] On the other side, another multicenter study investigating the consequences of switching from VPA to alternative ASMs and analyzing seizure outcomes at 12 and 24 months, showed that a GTCS worsening/recurrence occurred in 24.6% and 32.6% women at 12 and 24 months, respectively.[20]

Another significant deterrent to VPA withdrawal was a history of TCSs (both generalized and focal to bilateral), reflecting the known efficacy of VPA specifically against these hazardous seizures. In addition, a daily VPA dose greater than 900 mg, was associated, albeit weakly, with continuation, probably reflecting a subset of women with more severe epilepsy.

It is also important to highlight that any decision to shift or withdraw an ASM should be a shared one. Several studies indicate women's reluctance to change their VPA treatment after discussing the associated risks and benefits. In a Polish cohort study,[26] which aimed to establish the reasons for continued use of VPA in a cohort of WWE, it was found that 109 of 353 women continued to use VPA and that ~60% of these WWE did not agree to discontinue VPA after thoroughly considering the potential risks, whereas the other 40% continued using VPA because pregnancy was highly unlikely and/or other treatments failed. Similarly, a cross-sectional study[27] conducted in the United Kingdom found that 79% of patients elected to continue VPA treatment after receiving explanations. A Catalan cohort study[28] involving 60 women revealed that 68.3% continued VPA treatment after discussing the risks and benefits, citing ID, no reproductive desire, and fear of seizure recurrence as the main reasons for not changing treatment. Due to the retrospective nature of the study, we could not collect data on how women's preferences

influenced VPA prescriptions. However, the continuation rates observed in these studies are very similar to ours.

In our study, in a univariate analysis, VPA withdrawal was associated with a threefold increased risk of seizure worsening, considering all seizure types, and a fivefold increase, considering TCSs only. This finding was further confirmed by multivariate analysis, which demonstrated an almost threefold increased risk of TCS worsening, regardless of the type of epilepsy. Due to the small sample size, we could not identify specific factors linked to seizure worsening in the withdrawal cohort. However, across the entire population, focal EDs, focal seizures, and focal epilepsy were the most significant determinants of seizure relapse, followed by high seizure frequency and polytherapy, consistent with the existing literature.[29–32]

4.1 | Strengths and limitations

Our study has certain limitations. First, its retrospective nature introduces the possibility of selection bias, confounding factors, and missing data. In addition, the population studied may not be representative of all WWE due to the inclusion of patients from secondary and tertiary epilepsy clinics. Second, there is inhomogeneity within the cohorts, particularly the relatively small size of the withdrawal cohort compared to the others.

Conversely, the main strengths of our study lie in its multicenter design, the inclusion of a substantial number of participants, and the consideration of all types of epilepsy.

5 | CONCLUSIONS

Following the EMA restrictions on VPA use in WOCP, the vast majority of women treated with VPA at eight specialized epilepsy centers in Italy did not undergo a change in therapy. This likely reflects a population with severe epilepsy, where VPA is challenging to replace, whereas women with milder forms of epilepsy likely discontinued VPA earlier, as indicated by its low overall prescription frequency.

It is important to note that women who discontinued VPA from a polytherapy regimen without transitioning to another ASM experienced a threefold increase in the risk of seizure exacerbation, particularly TCSs.

AUTHOR CONTRIBUTIONS

R.E. contributed to data collection and drafted a substantial portion of the manuscript and figures. B.M. was involved in the study's conception and design, wrote the study protocol, coordinated data collection and analysis, and contributed to manuscript drafting. E.Z., A.L.N., L.G., F.R., G.M., and C.A.G. contributed to the study's conception, design, and data collection. G.F., E.C.I., F.B., K.T., C.C., D.P., and V.T. assisted with data collection. L.M.B.B. performed the statistical analysis. All authors critically reviewed the manuscript, approved the final version, and take responsibility for the accuracy and integrity of this work.

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CONFLICT OF INTEREST STATEMENT

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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.

ETHICS STATEMENT

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.

ORCID

Roberta Esposto https://orcid.org/0009-0000-5972-2102
Giovanni Falcicchio https://orcid.org/0000-0003-0745-5246
Emanuele Cerulli Irelli https://orcid.org/0000-0003-3906-555X
Loretta Giuliano https://orcid.org/0000-0003-2512-6972
Katherine Turner https://orcid.org/0000-0001-7268-4681
Francesca Bisulli https://orcid.org/0000-0002-1109-7296
Barbara Mostacci https://orcid.org/0000-0003-4851-2796

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APPENDIX A

Epilepsy and Gender Commission of the LICE (Italian Chapter of the ILAE)

Giulia Battaglia, Neurologia universitaria, IRCCS Policlinico San Donato, Piazza Malan 2, 20097 San Donato, Milanese (MI), Italy; Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, and Epilepsy Society, Chalfont-St-Peter, Bucks, United Kingdom.

Leonilda Bilo, Epilepsy Center, University of Napoli "Federico II", Napoli, Italy.

Gaetano Cantalupo, U.O.C. di Neuropsichiatria Infantile, Dipartimento ad Attività Integrata Materno Infantile—AOUI di Verona, Full Member of the ERN EpiCARE, Verona, Italy; Child Neuropsychiatry, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona; Centro Ricerca per le Epilessie in età Pediatrica (CREP), Azienda Ospedaliera Universitaria di Verona, Verona, Italy.

Vania Durante, Neurology Unit, "A. Perrino" Hospital, Brindisi, Italy.

Caterina Ermio, Department of Neuroscience, "S. Giovanni Paolo II" Hospital, Lamezia Terme, Catanzaro, Italy.

Carlo Andrea Galimberti, Epilepsy Center, IRCCS Mondino Foundation, Pavia, Italy.

Sara Gasparini, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy; Regional Epilepsy Centre at Great Metropolitan Hospital, Via Melacrino, Reggio Calabria, Italy.

Loretta Giuliano, Department of Medical, Surgical Sciences and Advanced Technologies G.F. Ingrassia, Section of Neurosciences, University of Catania.

Angela La Neve, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Bari, Italy.

Barbara Mostacci, IRCCS Istituto delle Scienze Neurologiche di Bologna, Full Member of the ERN EpiCARE, Bologna, Italy.

Giulia Monti, Neurology Unit, Ospedale Ramazzini di Carpi, AUSL Modena, Italy.

Bruna Nucera, Department of Neurology, Hospital of Merano (SABES-ASDAA), Merano, Italy.

Irene Pappalardo, Division of Neurophysiology and Epilepsy Centre, IRCCS San Martino Policlinic Hospital, Genoa, Italy.

Federica Ranzato, Epilepsy Center, Vicenza Hospital, Italy.

Elena Zambrelli, Epilepsy Center—Sleep Medicine Center, Childhood and Adolescence Neuropsychiatry Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, Milan, Italy.