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FULL-LENGTH ORIGINAL RESEARCH

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Doing without valproate in women of childbearing potential with idiopathic generalized epilepsy: Implications on seizure outcome

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Abstract

Objective: Valproate (VPA) use in women with idiopathic generalized epilepsy (IGE) who are of reproductive age has been a matter of concern and debate, which eventually led to the recent restrictions by regulatory agencies. The aim of our study was to investigate the relationship between VPA avoidance/switch and seizure outcome in women of childbearing potential.

Methods: We retrospectively reviewed data from female patients with IGE, 13-50 years of age, followed since 1980. We evaluated the prescription habits, and the rate of VPA switch for other antiepileptic drugs (AEDs) and its prognostic implications. Seizure remission (SR) was defined as the absence of any seizure type more than 18 months before the last medical observation. The main aim of the study was to assess (a) possible changes in seizure outcome related to VPA switch for other AEDs, especially in patients planning a pregnancy; and (b) possible differences in SR based on the presence/absence of VPA at last observation.

Results: One hundred ninety-eight patients were included in the study. Overall SR at last medical observation was 62.7%. SR significantly differed between subjects taking and those not taking VPA ($P < .001$) at last visit. Multiple regression models showed that taking VPA at last medical observation was strongly associated with SR in both the general population ($P < .001$) and the juvenile myoclonic epilepsy (JME) group ($P < .001$). Thirty-six (70.6%) of 51 patients who switched from VPA during follow-up experienced a clinical worsening. Switching back to VPA was more frequently associated with SR at last observation ($P < .001$). In those patients who substituted VPA in view of a pregnancy, SR and drug burden (monotherapy vs polytherapy) differed significantly before and after the switch.

Significance: Our study suggests that VPA avoidance/switch might be associated with unsatisfactory seizure control in women with IGE who are of childbearing potential. Our findings further highlight the complexity of the therapeutic management of female patients of reproductive age.

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KEYWORDS
idiopathic generalized epilepsy, pregnancy, reproductive age, restriction, valproate, women

1 | INTRODUCTION

Idiopathic generalized epilepsy (IGE) is a well-described form of epilepsy that is believed to have strong genetic bases.[1] It accounts for approximately 20% of the adult subjects who attend epilepsy outpatient clinics,[2] and is more common in women.[3] The heterogeneous IGE spectrum includes several syndromes that differ greatly in terms of clinical features and prognosis[4,5]; nevertheless, the goal of clinical remission can be achieved in up to 70%-80% of the cases thanks to an appropriate therapy.[6] Valproic acid (or valproate [VPA]) has always been considered the gold standard for the treatment of most IGE syndromes,[7,8] given its extraordinary efficacy for all types of generalized seizures (absences, myoclonic, and tonic-clonic seizures).[9] However, over the past 10 years, several studies have shown that VPA administration in pregnant women is associated with a considerably higher risk of major congenital malformations and impaired postnatal motor, behavioral, and cognitive development.[10–16] Based on emerging evidence, worldwide regulatory agencies have strongly discouraged prescribing of VPA to women of reproductive age, and have recommended that those already taking VPA switch to other anti-epileptic drugs (AEDs).[17] However, to date, none of the other broad-spectrum AEDs, not even the most recently marketed ones, have proved to be as effective as VPA on all generalized seizures.[18–20] According to the International League Against Epilepsy (ILAE) recommendations, VPA should still be considered as first-line treatment when it is supposed to be the most effective medication for a specific epilepsy syndrome and once established that a future pregnancy is extremely unlikely.[21] Despite the clinical relevance of this topic, very few randomized controlled trials comparing the efficacy of different AEDs in IGE are currently available, and they are mostly limited to specific syndromes.[7,22] Moreover, no clinical study has thoroughly evaluated the relationship between seizure outcome and VPA avoidance/switch in women of childbearing potential since the recommendations of regulatory agencies were released.

The aim of our retrospective study was to assess the prescription habits and the clinical implications of VPA avoidance/replacement in terms of seizure outcome in a population of women with IGE in their reproductive age.

Key Points

- The treatment of female patients with IGE during reproductive age has always been challenging, especially after the restrictions of regulatory authorities on valproate (VPA) use
- Many patients switched from VPA to other antiepileptic drugs (AEDs) during follow-up for childbearing potential issues
- VPA switching often led patients, including those substituting VPA in view of a pregnancy, to clinical worsening
- In this specific population, taking VPA at last medical observation was strongly associated with seizure remission

2 | METHODS

In this retrospective multicenter study, we reviewed data from patients followed at Policlinico Umberto I and Neuromed Epilepsy Unit from 1980 to 2018. The study was developed in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) guidelines. Relevant data were obtained through the review of both clinical charts and a computerized database. Subjects were enrolled according to the following inclusion criteria: (a) female gender; (b) age ranging from 13 to 50 years; (c) diagnosis of IGE; (d) availability of a complete clinical documentation and ≥1 electroencephalography (EEG) recording; and (e) follow-up duration of at least 18 months.

For each patient, we collected demographic data, family history of epilepsy in first- or second-degree relatives, history of febrile seizures, psychiatric comorbidities, age at onset, seizure type, possible triggering factors, EEG features (including photosensitivity), and prior/concomitant drug regimens. According to commonly accepted criteria, the diagnosis of IGE was confirmed by three trained epileptologists (CIE, DBC, GAT) who independently revised the patients' electroclinical findings. According to the ILAE classification,[23] we further identified specific epileptic syndromes: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and IGE with generalized tonic-clonic seizures only (IGE-GTCS). However, to achieve a more accurate characterization, other clinical entities already included in the latest classification proposal,

were considered as well: namely, eyelid myoclonia with absences (EMA)[24,25] and IGE-undefined (the latter definition was only applied to not otherwise classified cases).

The main aim of the study was to assess the impact on seizure outcome of VPA presence (VPA+) or absence (VPA–) in the patients' drug regimen. We considered different clinical situations including (a) patients who avoided VPA at treatment beginning; (b) patients who switched from VPA to another AED, especially in view of a future pregnancy; (c) patients who switched back to VPA; and (d) patients who received VPA (as either add-on treatment or sequential monotherapy) during follow-up. We also evaluated the prescribing pattern of AEDs alternative to VPA and the reasons for VPA substitution.

Seizure remission (SR) was defined as the absence of any seizure type (myoclonic, absence, and generalized tonic-clonic seizures [GTCS]) over the 18 months prior to the last medical observation. For methodologic purposes, we defined absences and myoclonic seizures as "minor seizures."

2.1 | Statistical analysis

Data were tested for normal distribution using the Shapiro-Wilk test, resulting in generalized nonnormal distribution. Data were therefore presented as median (interquartile range [IQR]), and comparison across relevant groups was performed through Mann-Whitney *U* test or Wilcoxon signed-rank test. Categorical variables were presented as frequency (count) and compared across relevant groups through the Fisher exact test. Group tests were two-sided, with $P < .05$ considered statistically significant. To study the effect of VPA therapy on seizure outcome, multiple regression models were elaborated. In the first model (M1) we used VPA treatment at the end of the follow-up and ineffectiveness of any first-line monotherapy as potential predictors. All models were corrected for age, follow-up duration, photosensitivity, psychiatric comorbidity, history of febrile seizures, and specific syndrome (covariates). M1 model was applied to analyze three different outcomes: SR (M1a), persistence of GTCS (M1b), and polytherapy (>1 AED) (M1c) at final observation. We also elaborated a model (M2) in which we used VPA ineffectiveness at any time during follow-up as a possible predictor, with the same above-mentioned covariates. Analyses were performed and figures generated using R 3.5.1 (R Project for Statistical Computing).

3 | RESULTS

3.1 | General characteristics of the patient population

We reviewed data from 260 female patients diagnosed with IGE. Sixty-two subjects were excluded because they did not meet the inclusion criteria; therefore 198 patients were actually considered for analysis. The median age of the study participants was 29.84 years (IQR 22.79-40.25) and the median follow-up was 11.01 years (IQR 5.84-24.85). Follow-up duration was comparable among different epileptic syndromes except for CAE ($P = .021$). The timing of the first visit for all patients is illustrated in Figure 1, whereas 176 patients (88.9%) performed the last one in 2018. The most common syndrome was JME, diagnosed in 81/198 women (40.9%). Demographic and clinical data are summarized in Table 1.

3.2 | AED prescribing pattern at first observation

Valproate was the first-line treatment in 90 patients (45.5%), levetiracetam (LEV) in 51 (25.8%), lamotrigine (LTG) in

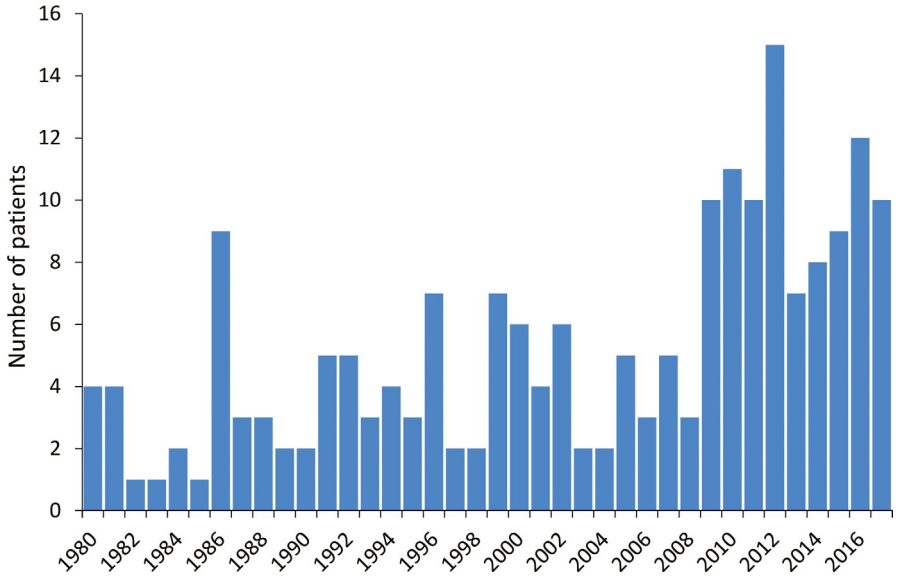

FIGURE 1 Distribution of patients according to the year of enrollment

Age, y, median (IQR)	29.84 (22.79-40.25)
Follow-up, y, median (IQR)	11.01 (5.84-24.85)
Family history in first and/or second relative degree, n, %	81, 40.9%
Psychiatric comorbidity, n, %	26, 13.1%
History of febrile seizures, n, %	18, 9.1%
Type of epilepsy	
Childhood absence epilepsy (CAE), n, %	11, 5.6%
Juvenile absence epilepsy (JAE) n, %	25, 12.6%
Juvenile myoclonic epilepsy (JME), n, %	81, 40.9%
Eyelid myoclonia with absences (EMA), n, %	20, 10.1%
IGE with generalized tonic-clonic seizures only (IGE-GCTS), n, %	43, 21.7%
IGE-undefined, n, %	18, 9.1%
EEG features	
Photoparoxysmal response (PPR), n, %	59, 29.8%

TABLE 1 Demographic and clinical characteristics

20 (10.1%), phenobarbital (PB) in 12 (6.1%), ethosuximide (ETS) in 4, and topiramate (TPM) in 2 (among the other AEDs, carbamazepine was used in 6 cases and clonazepam in 5).

3.3 | Drug regimen changes during follow-up

One-third (30/90) of patients receiving VPA as first-line AED continued to take it until the last medical observation, whereas 60 subjects (66.7%) switched from VPA to another medication during follow-up. Clinical reasons for switching are summarized in Figure 2, the most common (28/60) being the planning of a pregnancy. LEV and LTG were the most frequent alternatives to VPA after its discontinuation (in 45.1% and 25.5% of cases, respectively). The other AEDs chosen by physicians to replace VPA are shown in Table 2. Among 108 patients taking first-line AEDs other than VPA, 34 added VPA at some point during follow-up due to poor seizure control.

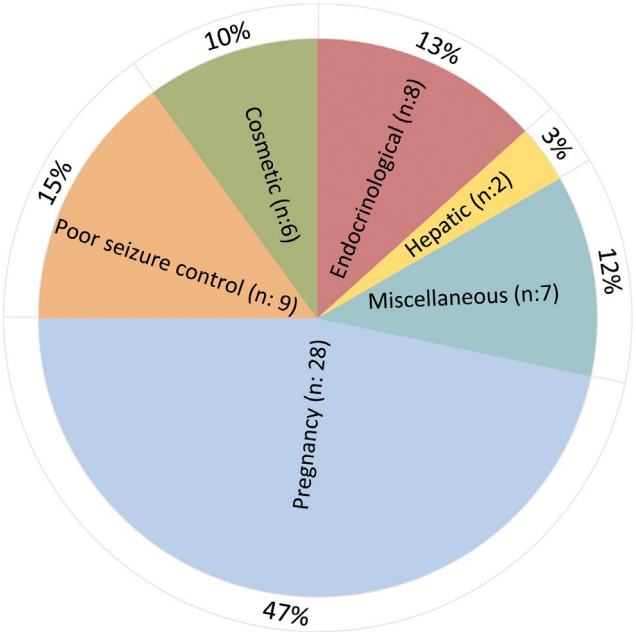

FIGURE 2 Reasons for switching from VPA to other AEDs in the overall population

3.4 | Clinical characteristics and outcome of patients who switched VPA during follow-up

Of 51 patients discontinuing VPA for causes other than poor seizure control, clinical worsening was documented in 36 (70.6%), 13 of whom (36.1%) switched back to VPA later on during follow-up. Patients who experienced a clinical worsening after VPA substitution and those who remained stable were comparable in terms of demographics, clinical features, and AED regimen. The rate of SR at last medical observation differed significantly between patients who switched back to VPA and those who did not (10/13%-76.9%- vs 3/23%-13%-, $P < .001$).

3.5 | Clinical characteristics and outcome of patients switching VPA in view of pregnancy

As previously stated, 28 patients switched VPA for another AED in consideration of a future pregnancy. In more than a half of cases (13/28, 53.6%) the switch occurred after 2014, with a median follow-up of 4 years (IQR 3-13.5). Before the switch, 23/28 patients (82.1%) were taking VPA as a monotherapy; 24/28 of patients were on SR while 4/28 were still experiencing "minor" seizures. Twenty of 28 patients (71.4%) presented a clinical worsening after switching (in most of them, seizures relapsed within 2-3 months), and 11

TABLE 2 AEDs used in substitution of VPA during switch

	Total of patients N = 51 pts	Worsening after VPA switch N = 36 pts	Stable after VPA switch N = 15 pts
Levetiracetam, n (%)	23 (45.1%)	16/23 (69.6%)	7/23 (30.4%)
Lamotrigine, n (%)	13 (25.5%)	9/13 (69.2%)	4/13 (30.8%)
Phenobarbital, n (%)	10 (19.6%)	7/10 (70%)	3/10 (30%)
Clonazepam, n (%)	2 (3.9%)	1/2 (50%)	1/2 (50%)
Topiramate, n (%)	2 (3.9%)	2/2 (100%)	0
Ethosuximide, n (%)	1 (2%)	1/1 (100%)	0

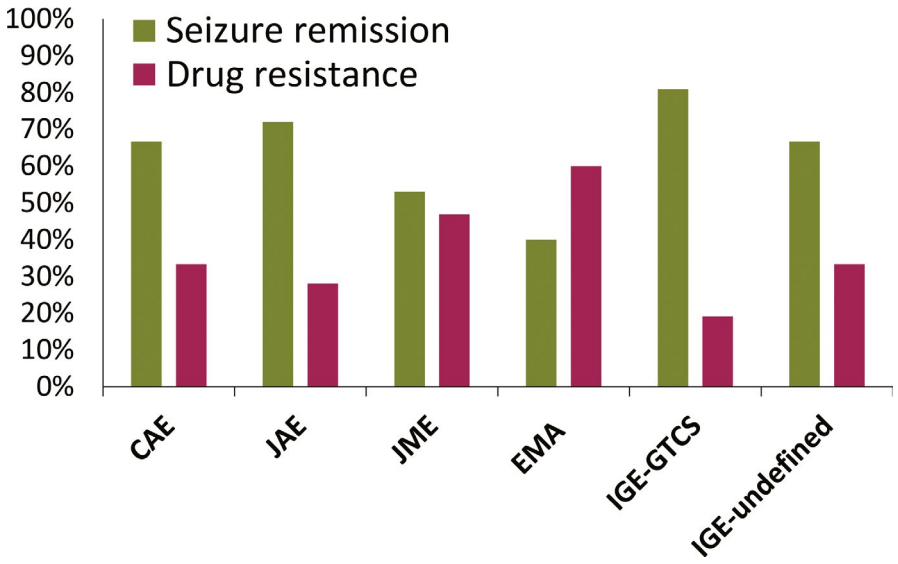

FIGURE 3 Seizure outcome at last medical observation according to different epilepsy syndromes

patients (39.3%) switched back to VPA during follow-up. As far as the drug burden is concerned, at last medical observation the number of patients taking monotherapy was significantly decreased when compared with the period before the switch (14/28 vs 23/28, $P = .02$). Considering seizure outcome, we observed a statistically significant difference in overall SR rate (15/28 vs 24/28, $P = .01$) and GTCS occurrence (5/28 vs 0/28, $P = .05$) at last medical observation when compared with the time before the switch.

3.6 | AED regimen and prognostic factors affecting seizure outcome at the last observation

On the final follow-up visit, 124 patients (62.6%) achieved SR, whereas 74 (37.4%) had persistent seizures. In the latter group, 32 patients (43.2%) still presented GTCS. Considering the different IGE syndromes, the lowest SR rate was observed in EMA (40%), and the highest in IGE-GTCS only (80.9%) (Figure 3). At last observation, 118 patients were on monotherapy, 61 were receiving two AEDs, 18 were taking three, and only one patient was on four medications. SR was observed in 63/80 subjects (78.7%) taking VPA and in 61/118 (51.7%) not taking it ($P < .001$) (Figure 4). Clinical and demographic characteristics of patients taking or not taking VPA at final observation are summarized in Table 3.

M1a showed that only a drug regimen including VPA at the end of follow-up was associated with SR (odds ratio [OR] 0.26, 95% confidence interval [CI] 0.12-0.53; <0.001). No single epileptic syndrome appeared significantly associated with a worse outcome in this model. However, when considering all syndromes with predominant myoclonic seizures, namely EMA and JME, as a single group, a trend to a worse prognosis was found (OR 2.36, 95% CI 0.93-6.82; $P = .08$). Moreover, significant differences in SR were documented in JME patients according to their "VPA status" (83.3% in the VPA+ group vs 35.3% in VPA- group; Fisher exact test $P < .001$) (Figure 4). Indeed, once restricted to JME patients, the M1a model showed that taking VPA at the final observation was strongly associated with SR (OR 0.09, 95% CI 0.02-0.31; $P < .001$).

M1b demonstrated that the ineffectiveness of any first-line monotherapy was associated with an increased risk of persistence of GTCS (OR 2.91, 95% CI 1.28-6.83; $P = .0124$), whereas age (OR 0.9, 95% CI 0.82-0.98; $P = .04$) and treatment with VPA appeared to be associated with GTCS freedom (OR 0.26, 95% CI 0.08-0.68; $P = .008$). Once again, when

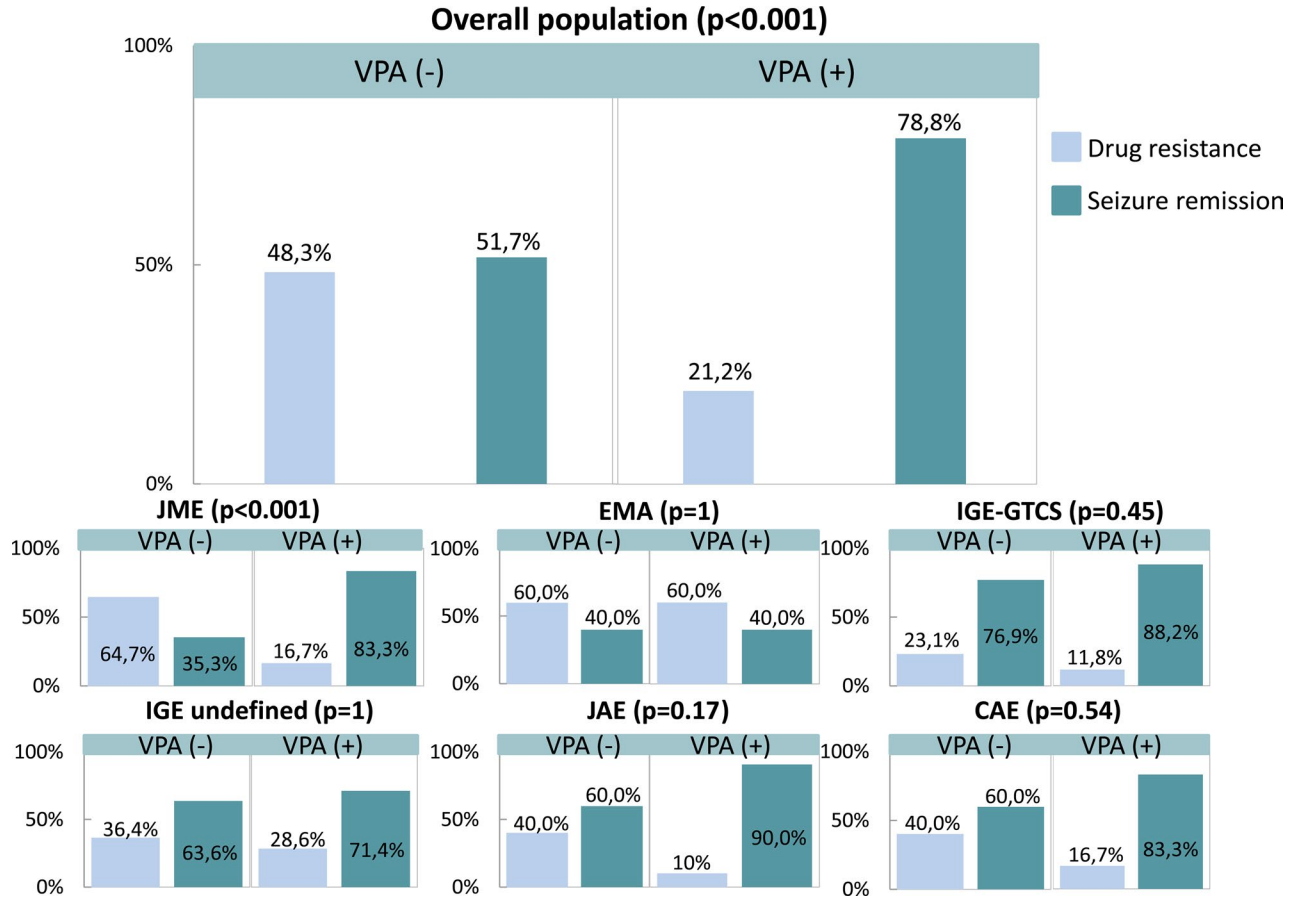

FIGURE 4 Seizure remission rate at last medical observation in the overall population (upper panels) and in specific epilepsy syndromes (lower panels) according to VPA status (VPA+ vs VPA-)

restricted to JME alone, M1b showed that VPA resulted to be associated with GTCS remission (OR 0.06, 95% CI 0.003-0.39; $P = .01$). Besides, M1c showed that the ineffectiveness of any first-line monotherapy predicted the need for polytherapy (OR 12.57, 95% CI 6.24-26.77; $P < .001$). No significant correlation was documented between either specific epileptic syndromes or clinical features and the necessity of a combination therapy.

Finally, M2 demonstrated that the VPA treatment ineffectiveness at any time during follow-up was significantly associated with polytherapy compared with the failure of other AEDs (OR 9.69, 95% CI 2.15-73.54; $P = .009$).

4 | DISCUSSION

To the best of our knowledge, this is the first study to explore the possible prognostic implications of VPA avoidance in women of childbearing potential. Despite the growing concerns about the possible consequences of restrictions on VPA use among female patients,[26–28] no study has yet assessed the potential impact of VPA avoidance/switch on seizure control.

As regards seizure outcome, persisting seizures were reported at the last observation by 37.4% of our patients, almost half of whom were still experiencing GTCS. The rate of remission in our population was lower than expected,[4,6] probably because this study included mainly patients with IGE persisting in adult life, who are more likely to achieve unsatisfactory seizure control.[29] Notwithstanding, in this special population, the avoidance/withdrawal of VPA could have been an additional determinant. Indeed, in our study, the SR rate at final observation differed according to "VPA status" (78.7% in the VPA+ group vs 51.7% in the VPA- group). Moreover, the regression models confirmed that the presence of VPA in the patients' drug regimen at final observation was the only factor strongly associated with SR (OR 0.26). Although age and follow-up duration were significantly different between VPA+ and VPA- patients, their potential influence on seizure outcome was ruled out by statistical analysis. VPA treatment at final observation was also found to be associated with freedom from GTCS, both in the overall population and in the JME group.

In addition to this, VPA ineffectiveness at any time (compared with other drugs) predicted the need for polytherapy at the end of follow-up (OR 9.69), suggesting an increased risk of unsatisfactory seizure control with alternative monotherapies.[29]

TABLE 3 Demographic and clinical characteristics of patients taking (VPA+) or not (VPA-) VPA at final observation

	VPA+ (80 pts)	VPA– (118 pts)	*P* value
Age, y, median (IQR)	31.6 (23.3-43.2)	26.2 (20.4-35.2)	**.004**
Follow-up, y, median (IQR)	17.6 (8.6-26.8)	7.9 (4.1-18.7)	**<.001**
EEG photosensitivity, n (%)	28	31	.2
Psychiatric comorbidity, n (%)	12	14	.5
Febrile seizures, n (%)	10	8	.2
Number of AEDs, n, mean	1.56	1.47	.32
Number of patients on polytherapy, n (%)	36 (46.15%)	44 (37.3%)	.27
CAE, n (%)	6 (7.5%)	5 (4.2%)	.29
JAE, n (%)	10 (12.5%)	15 (12.7%)	.96
JME, n (%)	30 (37.5%)	52 (44.1%)	.35
EMA, n (%)	10 (12.5%)	10 (8.5%)	.35
IGE-GTCS, n (%)	17 (21.2%)	26 (22%)	.89
IGE-undefined, n (%)	7 (8.8%)	10 (8.5%)	.94

Note: Bold indicates the statistical significance values.

In our work, the rate of SR in the VPA- group (51.7%) was dramatically lower than that reported in previous studies focusing on IGE prognosis.[4,6] This discrepancy suggests that VPA avoidance might determine a less favorable seizure control in female patients. However, this observation should be cautiously interpreted, in light of the several limitations of this study such as its retrospective nature and the possible selection bias.

Our data appear to be in line with the criticism provided by the recent ILAE position paper about the ban of VPA in childbearing age, especially in the management of more insidious epileptic syndromes. These considerations seem to be further supported by our results about the switch from VPA to other AEDs (and vice versa). Indeed, in the group of patients who switched VPA for other AEDs, the proportion experiencing clinical worsening was remarkable. Accordingly, a better seizure control was documented in the cohort of patients who switched back to VPA, when compared with patients who did not (76.9% vs 13%). The evidence of a large proportion of patients experiencing clinical worsening after VPA substitution was already reported by studies investigating the same issue in young women who withdrew VPA during pregnancy.[30]

In our work, the main reason for VPA substitution lay in the planning of a pregnancy. When focusing on these patients, we observed a lower SR rate and a higher drug burden (ie, polytherapy) at last observation with respect to the time preceding VPA switch. In the same group, poor seizure control justified VPA reintroduction in almost 40% of the cases. This observation seems to provide additional information about the debated topic of VPA use in this specific population,[31] highlighting the need for an accurate counselling, which especially deals with the risk of seizure worsening and the potential increase of drug burden.

Although our study provided some interesting results, it was limited by several factors including (a) the intrinsic bias depending on its retrospective design; (b) the challenging interpretation of the patients' outcomes due to the differences in follow-up duration within the study population; (c) a selection bias related to the enrollment of adult subjects followed in a tertiary epilepsy center, where a higher rate of drug resistance is usually expected; and (d) the poor availability of data concerning novel AEDs that were necessarily underprescribed in our cohort.

In conclusion, our study seems to suggest that doing without VPA can expose women with IGE to an increased risk of unsatisfactory seizure control. In light of these findings, clinicians should thoroughly discuss with their patients about potential risks and benefits of VPA avoidance, especially in cases of specific syndromic contexts (eg, JME). Overall, our data further highlight the need for alternative drugs that may ensure both effectiveness and safety in women of reproductive age with IGE. However, prospective studies on larger populations are warranted to provide more solid evidence.

CONFLICT OF INTERESTS

None of the authors has any conflict of interest to disclose. 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.

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