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Valproate and female patients: Prescribing attitudes of Italian epileptologists

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ABSTRACT

Introduction: After the European Medicines Agency (EMA) warning on the use of valproate (VPA) in female patients, we explored the antiepileptic drug (AED) prescribing attitudes of Italian epileptologists with regard to sex and VPA use in patients with epilepsy.
Material and methods: A specifically designed 30-item questionnaire was distributed at the annual multicenter meeting of the Italian League Against Epilepsy (LICE), held in Rome on January 2018. One hundred and sixty-nine physicians answered the questionnaire.
Results: In females, VPA was significantly less prescribed as first-choice AED in childhood absence epilepsy (22% females vs 64% males, $p < 0.001$), Dravet syndrome (54% vs 71%, $p = 0.01$), juvenile myoclonic epilepsy (JME) (2% vs 74%, $p < 0.001$), and undetermined epilepsy (0% vs 32%, $p < 0.001$). Ninety-six percent of the respondents inform teenage girls of the detrimental effects of intrauterine exposure to VPA; 74% recommend contraceptive measures when prescribing VPA. All the respondents stated that they were aware of the recommendations on VPA in female patients, and 64% claimed to have had difficulties in implementing them.
Conclusions: The main challenges were represented by women with JME, who were seizure-free on VPA and failed to respond to levetiracetam and lamotrigine, and by little girls for whom VPA was considered the best choice. According to many Italian epileptologists, the decision to withdraw VPA should be shared with the patient.

1. Introduction

Valproic acid (VPA) has been acknowledged over the last 30 years as the most teratogenic antiepileptic drug (AED), with an average dose-dependent risk of approximately 10% for major birth defects [1]. Moreover, in the last decade, several studies showed a significant relation between womb exposure to VPA and slightly impaired cognitive function in school and preschool children [2–14]. Behavioral disturbances and autism spectrum disorder were also found to be significantly increased after intrauterine exposure to VPA [3,10–12,14].

After the subsequent warning of the European Medicines Agency (EMA) [15–18], endorsed also by the Italian Drug Agency (Agenzia Italiana del farmaco; AIFA) [19], neurologists are currently prevented from prescribing valproate for epilepsy in girls and women of childbearing age unless other treatments are ineffective or not tolerated.

Nevertheless, several Authors questioned the advisability of indiscriminately withholding VPA in this population, mainly because of its effectiveness in generalized epilepsies, where alternative options are scanty [20,21] and to the subsequent consideration that women should have the same rights as men to receive the most effective treatment for their disease [22]. Noteworthy, pregnancy might not be an option for several women.

Little data exist on the impact of such evidence and recommendations on practice patterns in women with epilepsy. Common trends in different countries are a reduced prescription of valproate overall and

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lower prescribed doses together with increased use of lamotrigine (LTG) and levetiracetam (LEV) rather than carbamazepine (CBZ) or VPA [23–25]. The decline in use likely began before the warning in women with epilepsy, as one Swedish study showed [26]. Data on prescriptions for indications other than epilepsy are conflicting [26–29] with several studies demonstrating a rise. A recent review showed that adherence to recommendations on VPA use in reproductive-aged women remains quite low [30].

To our knowledge, these data come mainly from the studies on registries, while the prescribing attitudes of neurologists, and more specifically, epileptologists, in female patients, have never been assessed.

The present study was aimed at exploring the antiepileptic drug (AED) prescribing attitudes of Italian epileptologists with regard to sex, in particular valproate (VPA) use in female patients, and their possible difficulties in following the recommendations of EMA and AIFA.

2. Materials and methods

2.1. Study population

Every year in late January, a meeting of the Italian epileptologists belonging to the Italian chapter of the International League Against Epilepsy (ILAE) (Lega Italiana Contro l'Epilessia [LICE] — Italian League Against Epilepsy) is held in Rome. This "Polycentric Meeting" (Riunione Policentrica) is a Continuing Medical Education (CME) program, free of charge for those who renew their membership dues, traditionally attended by most Italian epileptologists and other health professionals involved in the care of people with epilepsy.

2.2. Study questionnaire

The LICE Commission on "Epilepsy and gender" designed a 30-item questionnaire (Supplement 1) and distributed it to all participants during the 2018 edition of the meeting, held on the 25th and 26th of January. The questionnaire was specifically addressed to physicians. A first part collected personal, educational, and professional data of the respondent. A second part inquired on attitudes and practice patterns of prescription of AEDs, with particular attention to valproate, in patients of different sex, in different clinical scenarios. Respondents were asked to answer only to questions related to the population they have actually dealt with in their practice (children or adults). The last questions dealt with knowledge of the EMA warning and possible difficulties in its implementation. The participants voluntarily filled in the questionnaire and returned it during the meeting. Being the participation anonymous and being the survey a quality improvement initiative of our scientific society, no ethics committee approval was required.

2.3. Statistical analysis

Categorical variables were presented as absolute and relative frequency (%). Chi-square test was used to evaluate the prescription difference between males and females and between juvenile myoclonic epilepsy (JME) and focal epilepsy. The test of interaction was evaluated for prescription differences between sex and the general characteristics of the respondents. p-Values <0.05 were considered significant.

3. Results

Three hundred and ninety-five people attended the meeting. Among them, 215 applied for the CME credits as specialized physicians. One hundred and sixty-nine questionnaires were returned, 156 of which filled in by specialists, 13 by residents. General information on respondents is reported in Table 1.

Several significant differences were found in the prescribing patterns between male and female patients. Table 2 shows the first-choice drug in several different clinical scenarios involving children and adolescents. These questions were specifically addressed to 125 respondents who stated they treat (at least "seldom") children and adolescents.

Table 1
General characteristics of the respondents.

Characteristics	Number (%)
Age — mean (SD), range	47.0 (11.6), 25–72
Sex — Female	109 (64.5)
Geographic area of practice:	
Northern Italy	83 (49.1)
Central Italy	40 (23.7)
Southern Italy/Islands	46 (27.2)
Area of specialization:	
Adult neurology	91 (53.9)
Child neurology	64 (37.9)
Other	14 (8.2)
Experience in epileptology (years):	
≤10	63 (37.3)
11–20	47 (27.8)
21–30	29 (17.2)
31–40	24 (14.2)
No experience	6 (3.5)
Main occupation area:	
Hospital	143 (85.1)
Outpatient clinic	21 (12.5)
Research	4 (2.4)
Work in an epilepsy center — yes	111 (66.7)

Questions 21, 22, and 23 dealt with sharing information on possible detrimental effects on the offspring when prescribing VPA to teenage girls, and on the concomitant prescription of contraceptive measures. Less than 10% of the respondents to the three questions stated they never prescribe VPA to teenage girls. The majority of the remaining respondents always informs the patients and tell them it is advisable to switch to another AED when considering a pregnancy. Namely, 112/117(96%) inform on the teratogenic risk and 112/118 (95%) on the possible cognitive effects. Eighty-six out of 116 (74%) always prescribe contraceptive measures when prescribing VPA. Multiple answers were not considered.

Some questions were specifically addressed to 118 respondents who stated they treat (at least "seldom") adults. Fig. 1 shows their evaluation of the prescriptive appropriateness in women with JME or focal epilepsy who were seizure-free on VPA and failed to respond to LEV and LTG (JME), or CBZ and LEV (focal epilepsy).

When asked about the appropriate behavior in seizure-free women taking VPA at the 7th week of gestation, 74/118 respondents (63%) considered it appropriate to continue VPA at the minimum effective dose, 23 (19.5%) at the same dose (informing of the detrimental effects to the fetus), 10 (8.5%) considered it appropriate to switch to another AED, 4 (3%) to withdraw VPA (and inform about the relapse risk), and 7 (6%) did not answer or gave multiple answers.

All the 163 respondents stated that they were aware of the recommendations on VPA in female patients (6 missing); 64% stated they found difficulties in implementing them in their clinical practice. Fig. 2 shows data on reported difficulties taking into account only the answers of the respondents, who, consistently with the instructions, gave a single answer (83 respondents).

Prescribing patterns did not significantly differ in respondents of different sex, age, area of specialization, geographic area of practice, and experience in epileptology.

4. Discussion

Attitudes and prescriptive patterns of Italian epileptologists showed significant differences according to the patient's sex. Ethosuximide or LEV were considered the best first choices for girls with childhood absence epilepsy (CAE) or JME, while VPA was considered the best first-choice AED for boys with CAE or JME. As for treatment of undetermined

Table 2
Differences in prescribing attitudes between male and female patients with epilepsy.

Clinical scenario	First-choice AED	Males No. (%)	Females No. (%)	p value
CAE 8 years old	Lamotrigine	1 (0.8)	10 (8.0)	<0.001
	Ethosuximide	36 (28.8)	73 (58.4)	
	Valproic acid	80 (64.0)	27 (21.6)	
	Other/multiple choice	2 (1.6)	7 (5.6)	
	Missing	6 (4.8)	8 (6.4)	
Dravet syndrome 8 years old	Lamotrigine	0 (0)	4 (3.2)	0.0026
	Topiramate/zonisamide	14 (11.2)	25 (20.0)	
	Valproic acid	89 (71.2)	68 (54.4)	
	Other/multiple choice	6 (4.8)	10 (8.0)	
	Missing	16 (12.8)	18 (14.4)	
Self-limiting focal epilepsy 8 years old	Lamotrigine	2 (1.6)	4 (3.2)	0.228
	Carbamazepine/oxcarbazepine	43 (34.4)	49 (39.2)	
	Valproic acid	11 (8.8)	3 (2.4)	
	Levetiracetam	17 (13.6)	17 (13.6)	
	Other/multiple choice	37 (29.6)	36 (28.8)	
	Missing	15 (12.0)	16 (12.8)	
JME 15 years old	Lamotrigine	2 (1.6)	22 (17.6)	<0.001
	Valproic acid	92 (73.6)	2 (1.6)	
	Levetiracetam	23 (18.4)	87 (69.6)	
	Other/multiple choice	3 (2.4)	8 (6.4)	
	Missing	5 (4.0)	6 (4.8)	
Undetermined epilepsy 15 years old	Lamotrigine	10 (8.0)	20 (16.0)	<0.001
	Carbamazepine/oxcarbazepine	7 (5.6)	7 (5.6)	
	Topiramate/zonisamide	4 (3.2)	7 (5.6)	
	Valproic acid	40 (32.0)	0 (0)	
	Levetiracetam	50 (40.0)	74 (59.2)	
	Other/multiple choice	3 (2.4)	6 (4.8)	
	Missing	11 (8.8)	11 (8.8)	

CAE, Childhood Absence Epilepsy; JME, Juvenile Myoclonic Epilepsy.

epilepsy, more than one-third of respondents would choose VPA in males only. Although the difference was still significant, VPA was considered as first-choice drug for both boys and girls with Dravet syndrome. These results indicate a widespread attitude to avoid VPA as a first-choice drug in female patients, in keeping with EMA and AIFA warnings, according to which VPA should never be started even in prepuberal girls, unless alternative treatments are not suitable. Nonetheless, as several authors, including an ILAE Task force, pointed out [31] there are several situations in which the use of VPA can be still considered the most reasonable choice even in females. For patients with CAE, in fact, ethosuximide and valproate are the most effective drugs according to a network metanalysis [32]; moreover, the majority of patients do not need drug treatment in fertile age [33]. Therefore, denying VPA therapy to a girl with CAE might lead to an unjustifiable risk

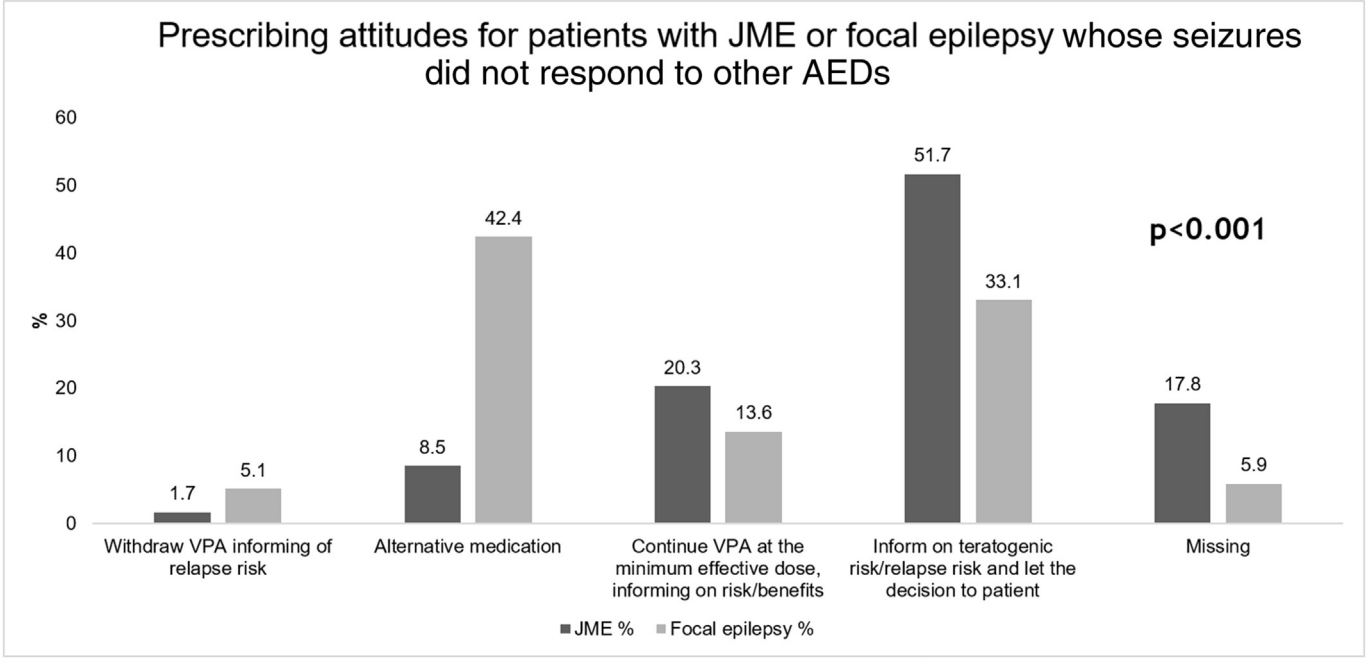

Fig. 1. Prescribing attitudes of physicians in women with Juvenile Myoclonic Epilepsy (JME) or with focal epilepsy, seizure-free on VPA whose seizures did not respond to other AEDs.

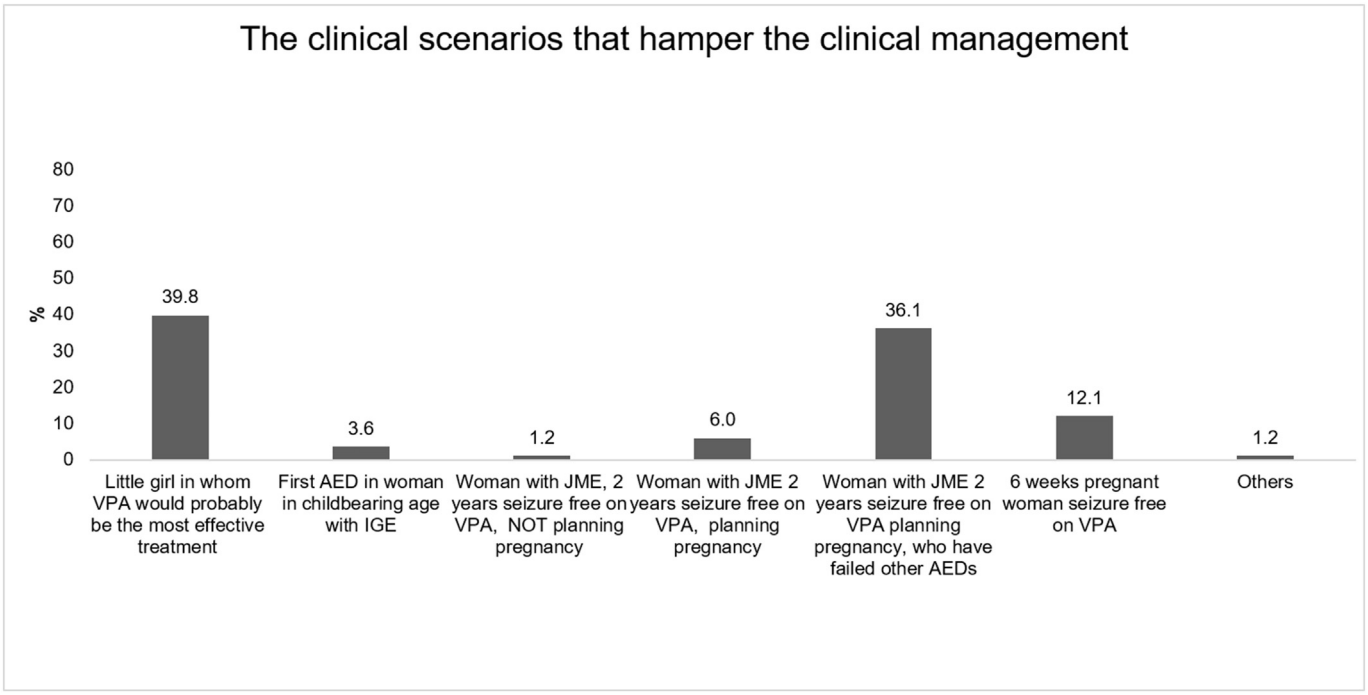

Fig. 2. The clinical scenarios that hamper the clinical management. AEDs, antiepileptic drugs; IGE, idiopathic generalized epilepsy; VPA, valproic acid; JME, Juvenile Myoclonic Epilepsy.

of a less effective treatment in female patients compared with that in males. Analogously, albeit for very different reasons, in Dravet syndrome, where the most effective treatment includes valproate, in combination with clobazam and stiripentol [34] and in which the presence of a genetic transmissible severe epilepsy and significant learning disability makes the chances of parenthood unlikely, the choice to exclude valproate as therapeutic option in female patients may be responsible for an unwarranted poor seizure control in a condition that, in addition, carries a significant risk of sudden unexpected death in epilepsy (SUDEP).

Consistently with the previous considerations, the clinical scenario of a female child or girl in whom VPA is probably the most effective drug was considered the most difficult to manage following the EMA/AIFA recommendations.

A large majority of epileptologists inform female adolescents of the adverse effects of intrauterine exposure to VPA; 74% always prescribe contraceptive measures. This gap is probably due to a proportion of women with severe diseases, making pregnancy unlikely. The patients' possible refusal of contraception for personal or religious beliefs should also be taken into account.

Significant differences were found in prescribing attitudes for women with focal epilepsy or JME being seizure-free with VPA after having failed other AEDs. In particular, switching to an alternative medication was the most common choice in patients with focal epilepsy, while it was an option only for 10% of the respondents for patients with JME. This reflects the limited therapeutic options available for generalized epilepsies [20,21]. When the clinical scenario of a woman with JME, responding to VPA and already failing other drugs, was complicated by planning a pregnancy, the decision was considered very challenging by the epileptologists. Under these circumstances the majority of the respondents would inform the patient on the risk benefit ratio in case of discontinuation/substitution, in order to help her make a thoroughly informed decision. Noteworthy, a shared decision after informing the patient was chosen by almost 40% of respondents also in case of focal epilepsy. The issue of the informed consent to treatment is particularly relevant, and it has been claimed that banning the use of VPA without the individual women's consent would be a violation of their rights [22]. As a matter of fact, faced with the choice, several people could put their personal safety over teratogenicity concerns, and the risk of seizure relapse might not be negligible. A survey of women's preferences would be valuable in this context. To add complexity, information on many newer AEDs are still largely insufficient, particularly on cognitive effects, and their use in pregnancy should always be considered in light of potential benefits and disadvantages.

If a pregnancy has already started, most specialists would opt to continue VPA, either reducing or maintaining the usual dose. These data suggest that respondents are aware of the risk of seizure relapse during pregnancy. Indeed, according to the European Registry of Antiepileptic Drugs and Pregnancy (EURAP) register data, tonic–clonic seizures were twice as common when VPA was withdrawn or shifted to another AED during the first trimester of pregnancy [35]. Moreover, there is an important knowledge gap on whether reducing or withdrawing valproate during pregnancy could actually affect the offspring outcome.

One limitation of our study is that the real return rate of the questionnaires has been approximated by estimating the number of participating specialized physicians to those requiring CME, as the real number of physicians attending the meeting was not traceable because of its free access. With this approximation, the return rate should be 70%. A selection bias could not be ruled out with certainty as physicians more involved in women's issues or more informed on the warnings might be overrepresented among the respondents.

5. Conclusions

Our study demonstrated a very good knowledge of the valproate-related pregnancy issues and of the EMA and AIFA warnings in Italian epileptologists. They inform their patients of the detrimental effects of intrauterine exposure to VPA in virtually all cases. Sex is an important determinant of prescriptions and avoiding VPA as a first choice in women and girls is a well-established prescribing attitude.

However, many epileptologists reported difficulties in strict adherence to the warnings on VPA, particularly in situations in which well-grounded alternatives are lacking. Moreover, a significant number of Italian epileptologists prefer, at least in more challenging situations, a shared choice with the patient, rather than an a priori withdrawal of valproate.

It should not be overlooked that the prescription attitude to exclude valproate as therapeutic option in female patients may be responsible for a poorer seizure control compared to males. More information on first-line agents for generalized epilepsies and on safety of newer antiepileptic agents in pregnancy are therefore urgently needed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.05.024.

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Declaration of Competing Interest

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