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Prevalence of valproate prescriptions in women of childbearing age in certain regions of Russia

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ABSTRACT

Aim: The goal of this retrospective study was to analyze the proportion of women with epilepsy who had received valproate (VPA) prescriptions in certain regions of Russia in 2018.
Methods: This retrospective cross-sectional study was based on the IQVIA Russia longitudinal prescriptions (LRx) database and included all individuals with a documented epilepsy code (International Classification of Diseases, Tenth Revision [ICD-10]: G.40) from 13 regions in Russia who had received at least one prescription of an antiepileptic drug (AED). The prevalence of VPA prescriptions in female patients with epilepsy aged 16–45 years was analyzed by age group and epilepsy diagnosis code. A multivariate logistic regression model was used to study the association between predefined variables and the probability of having received a VPA prescription.
Results: We found a total of 15,412 patients with epilepsy aged 16–45 who had received AED prescriptions in 2018 in the LRx database; 4488 (29.1%) of those patients were women. Of those, 64% had received at least one VPA prescription in 2018. The highest prevalence of VPA prescriptions was found in the age group 16–20 years (69%). This prevalence decreased with age. When compared with women aged 41–45 years, the 16–20-year-old age group was associated with a 1.6-fold increased probability of having receiving a VPA prescription (odds ratio [OR]: 1.60; $p < 0.001$), followed by the 21–25-year-old age group (OR: 1.46; $p < 0.001$). Nevertheless, the majority of women received VPA in low dosages (below 700 MG per day).
Conclusions: The prevalence of VPA prescriptions in women of childbearing age was quite high in Russia. The therapeutic doses were in line with international guidelines and had low teratogenic potential. Further research is needed to gain a better understanding of the reasons for prescribing VPA to women with epilepsy who are of childbearing age.

1. Introduction

Valproate (VPA) is considered one of the best options for the treatment of generalized epilepsy [1]. However, prospective studies have found evidence that VPA is associated with birth defects, reduction in intelligence quotient (IQ), and risk of developmental disabilities in children whose mothers took VPA while pregnant [2–7]. Recommendations in different languages are available to prescribers and patients in various countries. Since VPA is one of the most efficient drugs for treating generalized epilepsy, it is not always easy to avoid prescribing it to any women who may become pregnant.

Various studies, which have been conducted and published worldwide, have shown a decline in the number of prescriptions of VPA issued to women of childbearing age. Studies confirming this trend have been published in the UK [8], Ireland [9], Finland [10], Germany [11], Denmark [12], Lithuania [13], Sweden [14], and Australia [15].

Although VPA use in young women is declining, the proportions of women treated with VPA in several European countries are still relatively high [8–15]. This may be due to various reasons discussed in previously published studies [8–15]. One of the possible reasons may be the use of low VPA doses to minimize the teratogenicity risk of VPA, as this risk has been shown to be dose-dependent [16].

It is noteworthy that the prevalence of VPA use differs between countries. However, a valid comparison is difficult to obtain since researchers use different patient populations as well as different methods to estimate prevalence and incidence in their studies.

Epidemiological studies on epilepsy treatment and on VPA use, in particular, from Eastern European countries and Asia are lacking.

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Therefore, the goal of this retrospective study was to analyze the proportion of women with epilepsy who had received VPA prescriptions in certain regions of Russia in 2018.

2. Methods

The present retrospective cross-sectional study was based on the IQVIA Russia LRx database, which covers approximately 11% of all patients enrolled in federal or regional healthcare programs. The LRx database contains demographic and therapeutic data from 13 regions, including territories of Adygea, the Astrakhan region, Karachay-Cherkessia, Khakassia, Khanty-Mansi Autonomous Okrug, Krasnodar Krai, Krasnoyarsk Krai, the Kursk region, the Novgorod region, the Omsk region, the Sverdlovsk region, Yamalo-Nenets Autonomous Okrug, and Zabaykalsky Krai. The data were properly anonymized (in accordance with Federal Law 152) and included age, sex, diagnoses, and prescription information (indicating the trade name, molecule, drug form, dosage, manufacturer, region the drug was dispensed, and prescription period).

This study included all individuals with epilepsy documented by a diagnosis code (International Classification of Diseases, Tenth Revision [ICD-10]: G40) who had received at least one prescription of an antiepileptic drug (AED) (Anatomical Therapeutic Chemical [ATC] classification: N03). Patients with missing information regarding sex or age were excluded.

The outcome of the study was the prevalence of VPA prescriptions in female patients with epilepsy aged 16–45 years. The prevalence was analyzed by age group (16–20, 21–25, 26–30, 31–35, 36–40, and 41–45 years) and epilepsy diagnosis code (ICD-10: G40). Furthermore, the proportion of women who had received a combination of VPA and at least one other AED, specifically combinations of VPA and lamotrigine or carbamazepine, was estimated based on the evidence that these two combinations have been associated with the highest relative risk of major congenital malformations [16]. Finally, we calculated an average daily dosage and the proportion of women with a daily dosage below 700 MG, as this dosage is associated with a lower risk of congenital malformations [17].

We used a multivariate logistic regression model to study the association between predefined variables (age, physician specialty, epilepsy diagnosis) and the probability of VPA prescription in women aged 16–45 years. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using Statistical Analysis System (SAS) 9.4.

German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data. Because patients were only queried as aggregates and no protected health information was available for queries, no IRB approval was required for the use of this database or the completion of this study.

3. Results

We found a total of 15,412 patients aged ≥16 years who had received AED prescriptions in 2018 in the LRx database (mean age: 31.5 years (standard deviation [SD] = 21.9), 46.3% female). Of those, 4488 patients (29.1%) were women aged 16–45 years, and 42.2% were diagnosed with epilepsy without further specification, while 22.7% received a focal and 16.9% a generalized epilepsy diagnosis (Table 1).

Among women of childbearing age with epilepsy, 64% received at least one VPA prescription in 2018. This proportion was higher than in women over 45 (48%) and only a little lower than in men aged 16–45 years (68%) (Fig. 1). The highest VPA prescription prevalence in women of childbearing age was found in the age group 16–20 years (69%). This prevalence decreased with age (Fig. 2). Among women with generalized and other epilepsy, 67% received VPA; among women with focal or unspecified epilepsy, 63% were prescribed VPA (Fig. 3). When women received VPA, most of them (77.3%) used it as monotherapy, and 22.7% were treated with VPA in combination with at least one other AED. The combination of VPA and lamotrigine was very rarely prescribed (48 women; 1.1%). No women received the combination of VPA and carbamazepine. The most frequently prescribed drug in combination with VPA was topiramate, followed by levetiracetam and oxcarbazepine.

Table 1
Basic characteristics of study patients.

Variable	Patients with epilepsy (total) (N, %)	Women between 16 and 45 years (N, %)
Total	15,412	4488
Age (mean, SD)	31.5 (21.9)	29.6 (9.3)
Age group		
16–20	1648 (10.7)	1122 (25.0)
21–25	1208 (7.8)	547 (12.2)
26–30	1453 (9.4)	683 (15.2)
31–35	1661 (10.8)	790 (17.6)
36–40	1483 (9.6)	703 (15.7)
41–45	1372 (8.9)	643 (14.3)
46–60	3515 (22.8)	–
>60	3072 (19.9)	–
Female	8106 (52.6)	4488 (100%)
Male	7306 (47.4)	–
Epilepsy diagnosis		
Focal epilepsy (G40.0–G40.2)	3500 (22.7)	1013 (22.6)
Generalized epilepsy (G40.3, G40.4)	2602 (16.9)	790 (17.6)
Other epilepsy (G40.5–G40.8)	1334 (8.7)	380 (8.5)
Epilepsy, unspecified (G40.9)	6509 (42.2)	2305 (51.4)

SD = Standard Deviation

The average daily dosage of VPA was 445 MG (SD: 251 MG), and 85% of women received a daily dosage <700 MG (Fig. 4).

The results of the multivariate regression analyses are shown in Table 2. When compared with women aged 41–45 years, the 16–20-year-old age group exhibited a 1.6-fold increased probability of having received a VPA prescription (odds ratio [OR]: 1.60; $p < 0.001$), followed by the 21–25-year-old age group (OR: 1.46; $p < 0.001$). Focal epilepsy was associated with a slightly lower likelihood of having received a VPA prescription (OR: 0.84; $p = 0.007$).

4. Discussion

The main finding of this retrospective study was a fairly high prevalence of VPA prescriptions in women of childbearing age. In particular, the prevalence was highest in very young women (16–25 years). However, the daily dosage given to women of childbearing age was relatively low, and most women received VPA as monotherapy. As the study has a cross-sectional design and data were only available for one year, no investigation of prescription trends was possible to determine whether VPA use has been decreasing or whether the VPA prescription prevalence was higher some years ago than in 2018.

The relative contraindication for VPA in young women is well-known in Russia. Several current guidelines for physicians and booklets for patients are freely available in the Russian language. Karlov discussed the advantages and limitations of depakine compared with generics and other AEDs [18]. In 2015, Vlasov wrote that the prescription of VPA to young women requires a comprehensive assessment of possible therapy consequences, especially with regard to pregnancy planning [19]. In pregnancy, therapeutic approaches include the use of drugs with better safety profiles and lower teratogenic risks as well as dose adjustments [20]. Above all, as category D in the Food and Drug Administration (FDA) classification, the drug should be used with extreme caution in the first trimester of pregnancy [19]. Vlasov states that the use of VPA in women of childbearing age is justified if persistent

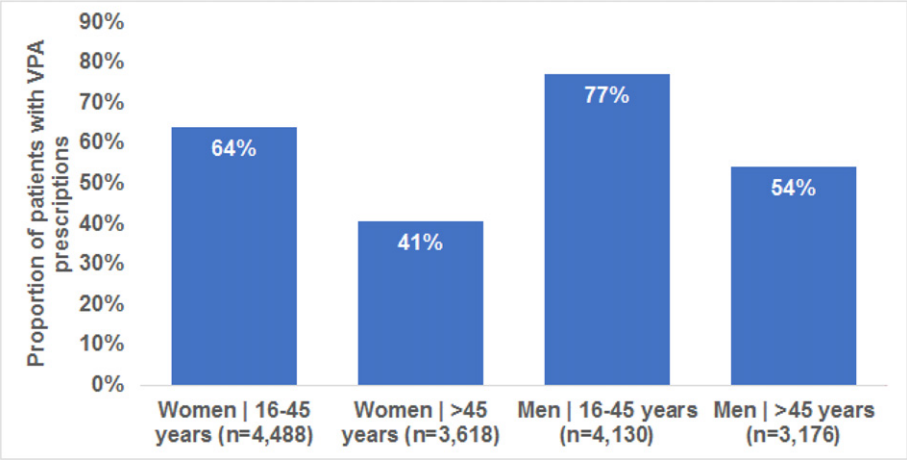

Fig. 1. Prevalence of patients with epilepsy who received at least one valproate prescription in certain regions of Russia.

remission is achieved on VPA, as well as when seizures, especially generalized convulsive seizures, are more clinically dangerous than the teratogenic effect of AED. The best solution for women of childbearing age on VPA is taking it as monotherapy, in the minimally effective dose, and in the form of extended-release preparations. The prescribing information for the use of valproic acid in the Russian language includes research data about its teratogenic potential and indicates that the drug should not be used in pregnancy or in women who may become pregnant unless absolutely necessary. This means that its use is recommended only in situations where other AEDs are ineffective or the patient does not tolerate them [21]. Women in Russia may use VPA during pregnancy, but this cannot be determined for certain in this study as no data regarding pregnancy are available. Therefore, the high proportion of VPA prescriptions in women of childbearing age in Russia is most likely due to its effectiveness for seizure prevention in generalized and other forms of epilepsy, as well as the absence of an absolute contraindication during pregnancy in spite of guidelines suggesting its use with significant limitations.

Few studies about the prevalence of VPA use, and not just trends in VPA use, are available. In Germany, in 2017, 23% of women aged 15–45 years received VPA. This proportion was much lower than in women older than 45 years but similar to men aged 15–45 years [11]. A study from the U.S. investigated 46,767 women with epilepsy aged 15 to 44 years and reported a VPA prevalence of 13.1% [22]. In a study from Poland, 30.9% of premenopausal women received VPA [23]. Based on these three examples, it is clear that the prevalence of VPA use strongly differs between countries. In fact, the proportion of young women treated with VPA in Poland was twice as high as in the U.S. and twice as high in Russia than in Poland, taking into consideration different study methods and definitions.

One possible explanation is the correlation between the proportion of all patients with epilepsy treated with a defined drug and young women treated with this drug. It can be assumed that the proportion of women who receive VPA is higher if the VPA share in the epilepsy therapy used in this country is higher. In a German study, 23% of young women received VPA. The proportion of all patients with epilepsy treated with VPA in Germany is about 28% [24]. In Russia, about 67% of patients with epilepsy receive VPA, while the prevalence of VPA use in young women is 64%. Why the overall prevalence of VPA use in Russia is much higher than in Germany is unclear since the same AEDs are available in both countries.

Different reasons may explain why young women decide to take VPA. They may not plan to have a child in the future because they already have children. Some women may not be willing to discontinue VPA because they have achieved long-lasting remission. In other cases, VPA may have been recommended to these women because an alternative treatment failed [25]. Some authors stress that VPA-induced fertile dysfunction is reversible; once the VPA dose was reduced or the drug was discontinued and substituted with a new-generation AED (lamotrigine, topiramate, etc.), reproductive function was restored, and more than 30% of women previously receiving VPA got pregnant [25,26]. Moreover, the data show that the prevalence of VPA use is

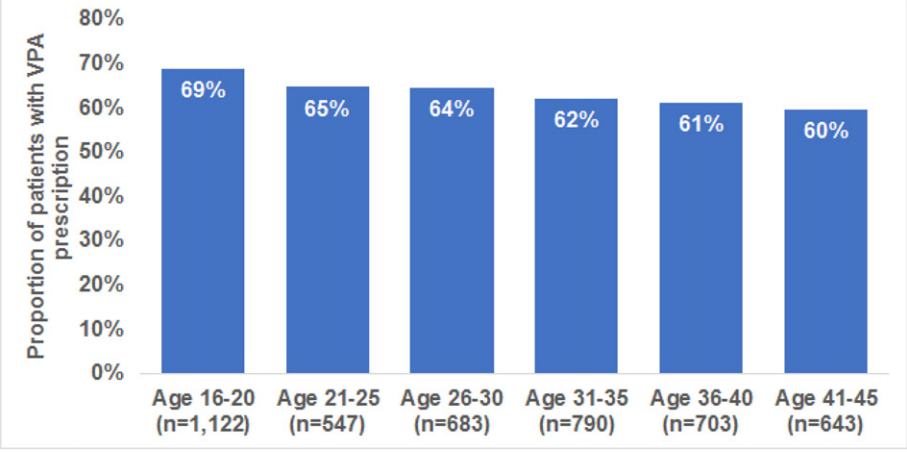

Fig. 2. Prevalence of females of childbearing age with epilepsy who received at least one valproate prescription in certain regions of Russia by age.

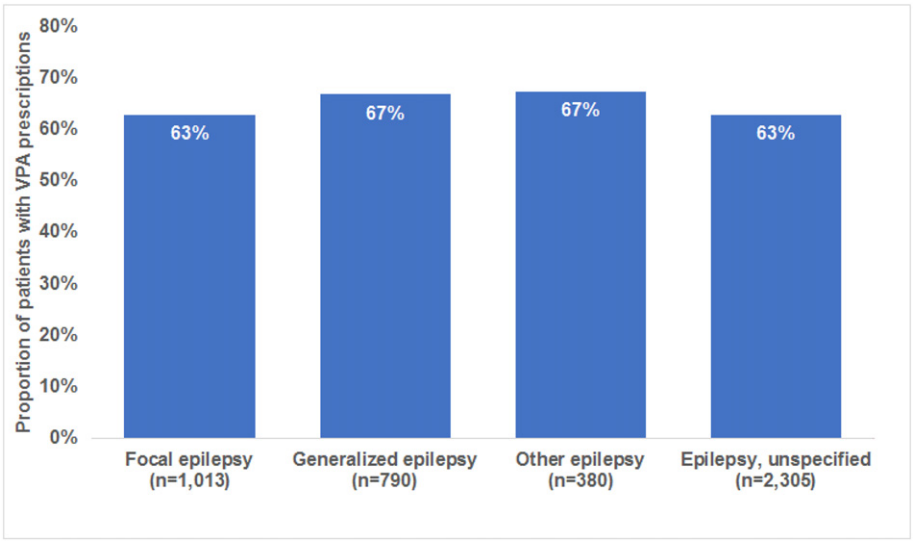

Fig. 3. Prevalence of females of childbearing age with epilepsy who received at least one valproate prescription in certain regions of Russia by epilepsy diagnosis (ICD-10 codes).

high not only in young women but also in young men. This may be explained by the higher prevalence of idiopathic forms of epilepsy in young patients, but this concept could not be investigated in this study as no exact diagnosis data were available.

This study has several limitations. The first limitation is the short time period of the investigation. A longer time period was not possible as LRx data in Russia have only been available from 2018 onward. Therefore, determining whether epilepsy of women treated with VPA had already failed to respond to other treatment alternatives is impossible. Second, the coverage of the LRx database amounts to only about 11%, and the database does not include many regions. Big cities with higher levels of care for patients with epilepsy, such as Moscow and St. Petersburg, could not be investigated in this study. There is a well-developed system of specialized care for patients with epilepsy in Moscow with regional and interregional centers, much more advanced than in other regions of the country. Routine electroencephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI) are available for free for patients with epilepsy almost within a couple of weeks. Third, the LRx database does not include any information on the reasons why physician decided to prescribe VPA to young women. Fourth, the database lacks information on the severity of the disease, including the frequency of seizures. Fifth, no hospital data were available. Sixth, no information about city or rural areas is available, which could play an important role in VPA therapy. For example, Guekht et al. have shown that, in Russia, new AEDs were prescribed mostly in big cities [27]. Seventh, valid information regarding the physicians prescribing AED was available only for some of the prescriptions and could not be analyzed in this study. We therefore cannot be sure whether VPA may or may not have been prescribed by psychiatrists as mood stabilizers. Eighth, the coding for the prescription is frequently meaningful for the broad category (ICD-10: G40) only. The clinical diagnosis is specified elsewhere in the medical documents, so we cannot rely on the diagnosis coded in prescriptions. Ninth, the duration for which VPA was taken was not assessed. Finally, the database does not contain information that allows investigating the prescription of VPA during pregnancy.

Nevertheless, the main strength of this study is that the LRx database contains real-world data, which allowed for an estimation of the prevalence of VPA prescriptions in Russia.

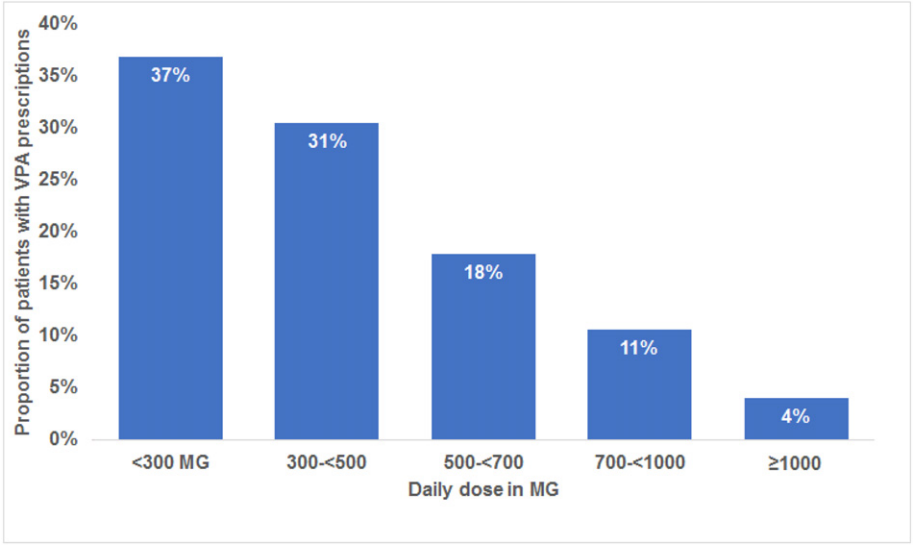

Fig. 4. Daily valproate dosage in females of childbearing age with epilepsy who received at least one valproate prescription in certain regions of Russia.

Table 2
Association of defined variables with the prescription of valproate in women of childbearing age (multivariate logistic regression).

Variable	OR (95% CI)[a]	p-Value
16–20	1.60 (1.35–1.89)	<0.001
21–25	1.46 (1.20–1.78)	<0.001
26–30	1.26 (1.05–1.52)	0.015
31–35	1.21 (1.02–1.45)	0.032
36–40	1.19 (0.99–1.42)	0.060
41–45	Reference	
Epilepsy diagnosis		
Focal epilepsy	0.84 (0.74–0.95)	0.007
Generalized epilepsy	1.03 (0.89–1.21)	0.659
Other epilepsy	1.11 (0.90–1.36)	0.324
Epilepsy, unspecified	Reference	

[a] Adjusted for age and epilepsy diagnosis.

5. Conclusion

The prevalence of VPA prescriptions in women of childbearing age was relatively high in Russia. However, the VPA doses were appropriate for women of childbearing age and in line with international guidelines. Further research is needed to gain a better understanding of the reasons for prescribing VPA to women with epilepsy who are of childbearing age.

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Author contributions

Karel Kostev contributed to the design of the study, performed the statistical analysis, managed the literature searches, and wrote the first draft of the manuscript. Galina Osina was responsible for data management, contributed to the design of the study, and corrected the manuscript. Alla Guekht verified the data and contributed to the data assessment and writing of the manuscript. Flora Rider verified the data and contributed to the assessment of data pertaining to healthcare provided to patients with epilepsy in Russia. All authors have contributed to and approved the final manuscript with regard to the functioning of the system of care for patients with epilepsy in Russia.

Declaration of competing interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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