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Prescription patterns of antiepileptic drugs in Kazakhstan in 2018: A retrospective study of 57,959 patients☆,☆☆

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ABSTRACT

Aim: The goal of this retrospective study was to analyze prescription patterns of antiepileptic drugs (AEDs) in Kazakhstan in 2018.
Methods: This study used prescription data of patients with epilepsy who received AEDs in Kazakhstan in 2018. The outcome of the study was the prevalence of use of several AEDs (i.e., valproate, carbamazepine, lamotrigine, topiramate, levetiracetam) in these patients. Demographic variables included age and sex. The present study used descriptive statistics only.
Results: In 2018, 57,959 patients with epilepsy with at least one AED prescription were found in the LRx database in Kazakhstan. The three most frequently prescribed AEDs were valproate (54.6%), carbamazepine (49.3%), and lamotrigine (16.8%). Interestingly, 10,745 valproate users were women aged ≤40 years. Monotherapy was more frequent than combination therapy and ranged from 80% in patients receiving topiramate to 90% in those receiving carbamazepine. The three most common combination therapies were valproate–carbamazepine (33.7%), valproate–lamotrigine (16.9%), and lamotrigine–carbamazepine (11.8%).
Conclusions: Patients with epilepsy were frequently prescribed valproate, carbamazepine, and lamotrigine in Kazakhstan in 2018. Further research is needed to gain a better understanding of the prescription of valproate in women with epilepsy who are of childbearing age.

1. Introduction

Approximately 46 million individuals had active epilepsy throughout the world in 2016 [1]. That same year, about 21 million people were affected by idiopathic epilepsy in low- and middle-income countries (LMICs). Epilepsy is associated with an increased risk of morbidity (e.g., injury [2], headache [3], depression [4]) and mortality [5] in this setting. Therefore, better treatment and management of patients with epilepsy in LMICs are urgently needed.

Antiepileptic drugs (AEDs) are effective treatments, and around two-thirds of patients with epilepsy who take AEDs are seizure-free [6]. Unfortunately, more than 50% of individuals with epilepsy do not receive appropriate treatment in LMICs, which may be related to inadequate skilled manpower, cost of treatment, cultural beliefs, or unavailability of AEDs [7]. In recent years, several studies have investigated prescription patterns of AEDs in LMICs [8–22]. Although these previous analyses have advanced the field, they are subject to some major limitations that should be mentioned. First, the sample size of most of the studies was small (i.e., less than 1000 participants) [8–16, 18–20]. Second, the majority of these studies included patients from hospital settings [8–16,19–22], and thus their findings may not be generalizable to private general and specialized practices. Third, the majority of this research was conducted in India or China [8,9,14,15,19,21], and little is known about the prevalence of AEDs in other LMICs. The only study on the treatment of epilepsy in Kazakhstan was published by Guekht et al. in 2017 [22].

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Therefore, the goal of this retrospective study was to analyze the prescription patterns of AEDs in Kazakhstan in 2018.

2. Methods

2.1. Database

The IQVIA LRx database accesses pharmacy data centers throughout Kazakhstan that process prescription data pertaining to all Kazakh patients benefiting from free healthcare (guaranteed volume of medical care). Data entries cover patient-specific data over time, such as anonymized identification number, age, sex, and prescription information (e.g., date of prescription, dispensing area, diagnosis, package information).

2.2. Study population

In 2018, 1,904,264 individuals were included in the LRx database in Kazakhstan. Among them, 58,544 patients were prescribed AEDs for any condition in 2018. This study focused on individuals receiving AEDs to treat epilepsy (Anatomical Therapeutic Chemical [ATC] Classification: N03).

2.3. Study outcomes and covariates

The outcome of the study was the prevalence of use of several AEDs in patients with epilepsy. These AEDs were valproate, carbamazepine, lamotrigine, topiramate, and levetiracetam. Demographic variables included age and sex.

2.4. Statistical analyses

This study used descriptive statistics only. Prescription patterns of several AEDs (i.e., levetiracetam, lamotrigine, valproate, carbamazepine, lacosamide, oxcarbazepine, topiramate) in patients with epilepsy were compared between Kazakhstan and Germany in 2018. Statistical analyses were performed with SAS 9.4.

3. Results

In 2018, 57,959 patients with epilepsy had been prescribed at least one AED in Kazakhstan. The mean age was 31.3 years (standard deviation [SD] 19.6 years), and 54.0% were men (Table 1). The three most frequently prescribed AEDs were valproate (54.6%), carbamazepine (49.3%), and lamotrigine (16.8%; Fig. 1). Interestingly, 10,745 valproate users were women aged ≤40 years. Monotherapy was more frequent than combination therapy and ranged from 80% in patients receiving topiramate to 90% in those receiving carbamazepine (Fig. 2). The three most common combination therapies were valproate–carbamazepine (33.7%), valproate–lamotrigine (16.9%), and lamotrigine–carbamazepine (11.8%; Fig. 3). We observed important differences regarding prescription patterns of AEDs in patients with epilepsy between Kazakhstan and Germany in 2018 (Table 2). In Germany, the three most frequently prescribed AEDs were levetiracetam (37.6%), lamotrigine (23.2%), and valproate (21.3%), while only 6.0% and 4.0% of individuals used lacosamide (not available in Kazakhstan) and oxcarbazepine (<0.01% in Kazakhstan).

4. Discussion

4.1. Main findings

In this retrospective study of almost 58,000 individuals with epilepsy, we found that valproate, carbamazepine, and lamotrigine were the most commonly prescribed AEDs in Kazakhstan in 2018. One major finding is that around 10,700 women aged ≤40 years received valproate, although this molecule is contraindicated in females of childbearing age. Furthermore, AEDs were usually prescribed as monotherapy. When they were prescribed as combination therapy, the most frequent combination therapy was valproate–carbamazepine. Finally, prescription patterns of AEDs in patients with epilepsy differed substantially between Kazakhstan and Germany in 2018.

4.2. Interpretation of the findings

In recent years, several studies have investigated prescription patterns of AEDs in LMICs [8–22]. A 2010 study including 278 seizure patients treated in a teaching hospital in India showed that the average number of AEDs prescribed per patient was 1.56, and that phenytoin (60.41%) and valproate (20.83%) were the most frequently prescribed AEDs in participants with idiopathic generalized epilepsy [8]. Another study of 336 adult patients with epilepsy from an outpatient epilepsy clinic in Ethiopia found that monotherapy accounted for approximately 80% of all AED prescriptions and that the two most common molecules were phenobarbitone (62.47%) and carbamazepine (17.91%) [16]. Finally, a Chinese multicenter cross-sectional study (N = 1603 participants) revealed that valproate was frequently prescribed as monotherapy to patients with generalized seizures (38.9%) and that oxcarbazepine was frequently prescribed to those with partial seizures (25.9%) [21]. In line with these studies, we observed that around 55% and 49% of AED users were prescribed valproate and carbamazepine, respectively. To the best of our knowledge, this retrospective study is one of the largest studies analyzing prescription patterns of AEDs in patients with epilepsy in LMICs and is one of the first studies to include participants from Kazakhstan.

One important result that deserves particular attention is the high number of women of childbearing age who were prescribed valproate. Valproate, a molecule marketed for the first time in France in 1967, potentiates the effects of γ-aminobutyric acid (GABA) in several regions of the brain involved in epilepsy [23]. Although valproate is an effective symptomatic treatment of epilepsy, it is a teratogenic drug, which means that pregnant women who receive this molecule are at an increased risk for giving birth to children with major malformations

Table 1
Basic characteristics of study patients.

Variable	Total	Valproate	Carbamazepine	Lamotrigine	Topiramate	Levetiracetam
N	57,959	25,983	20,807	5381	3409	2379
Age in years (mean, SD)	31.3 (19.6)	24.1 (18.9)	40.5 (17.8)	35.0 (17.2)	27.4 (18.2)	25.5 (18.1)
Age ≤ 10	18.2	30.7	4.4	6.6	23.0	26.5
Age 11–17	12.6	18.2	6.1	9.0	14.7	15.6
Age 18–30	21.2	19.2	21.3	28.6	21.8	23.4
Age 31–40	15.6	11.4	19.2	21.7	16.1	12.8
Age 41–50	12.6	8.6	17.7	13.9	11.2	9.5
Age 51–60	11.0	6.9	16.9	11.0	8.0	7.7
Age 61–70	6.4	3.6	10.4	6.9	4.0	2.9
Age > 70	2.5	1.4	4.1	2.0	1.8	1.6
Men	54.0	55.9	55.4	41.6	54.4	48.5
Women	46.0	44.1	44.6	58.4	45.6	51.5

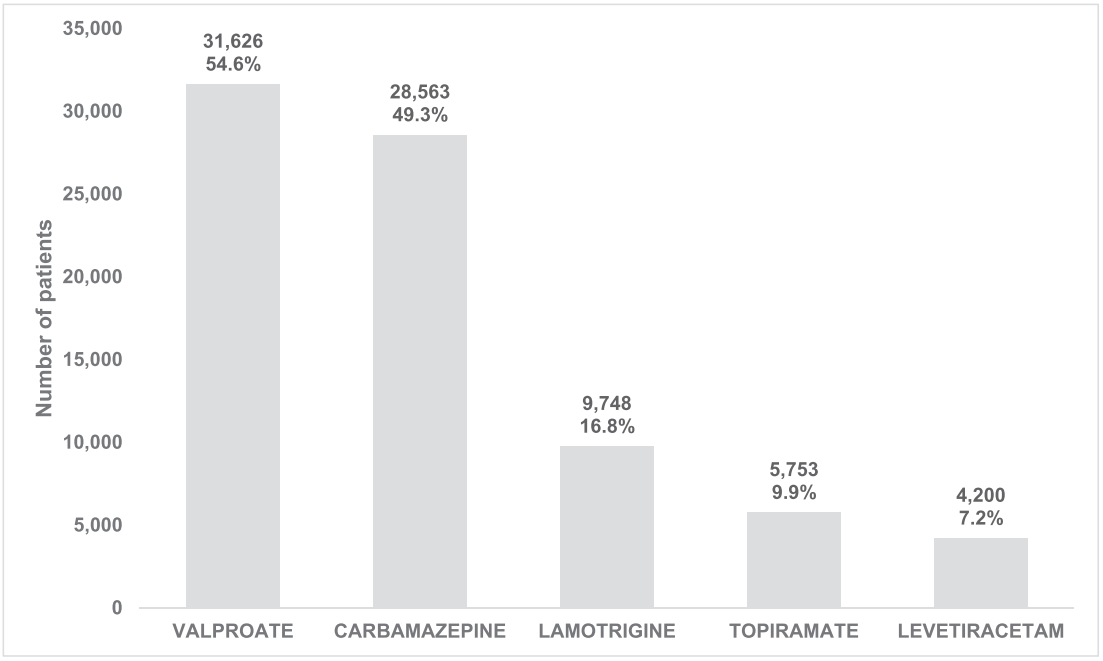

Fig. 1. Prevalence of prescription of AEDs in patients with epilepsy in Kazakhstan in 2018. Note: Total N was 57,959. Since patients may have received more than one drug at the same time (combination therapy), the sum of percentages is greater than 100%.

[24]. Moreover, an increasing number of studies has highlighted the additional deleterious impact of valproate on reproductive health, cognition, and behavior. For example, a 2008 randomized prospective study found that polycystic ovary syndrome was more frequent in valproate users than in lamotrigine users after 12 months of therapy [25]. A 2009 prospective, observational multicenter study further reported that in utero exposure to valproate was a risk factor for impaired cognitive function at three years of age [26]. Taken together, these findings clearly show that valproate should be avoided in women with epilepsy of childbearing age, and declining trends in valproate use have been observed in this population in several countries [27,28]. The fact that around 41% of individuals receiving valproate were women aged ≤40 years in our study is of particular concern, and future research should aim to identify the risk factors for valproate prescriptions in young women.

This retrospective study also showed that approximately 34% of patients receiving combination therapy were concomitantly prescribed valproate and carbamazepine. Before going any further, one should bear in mind that disease control is not reached with monotherapy for 30% to 40% of AED users [29]. Although the debate concerning the most effective combination therapies for the treatment of epilepsy is ongoing, using two molecules with complementary mechanisms of

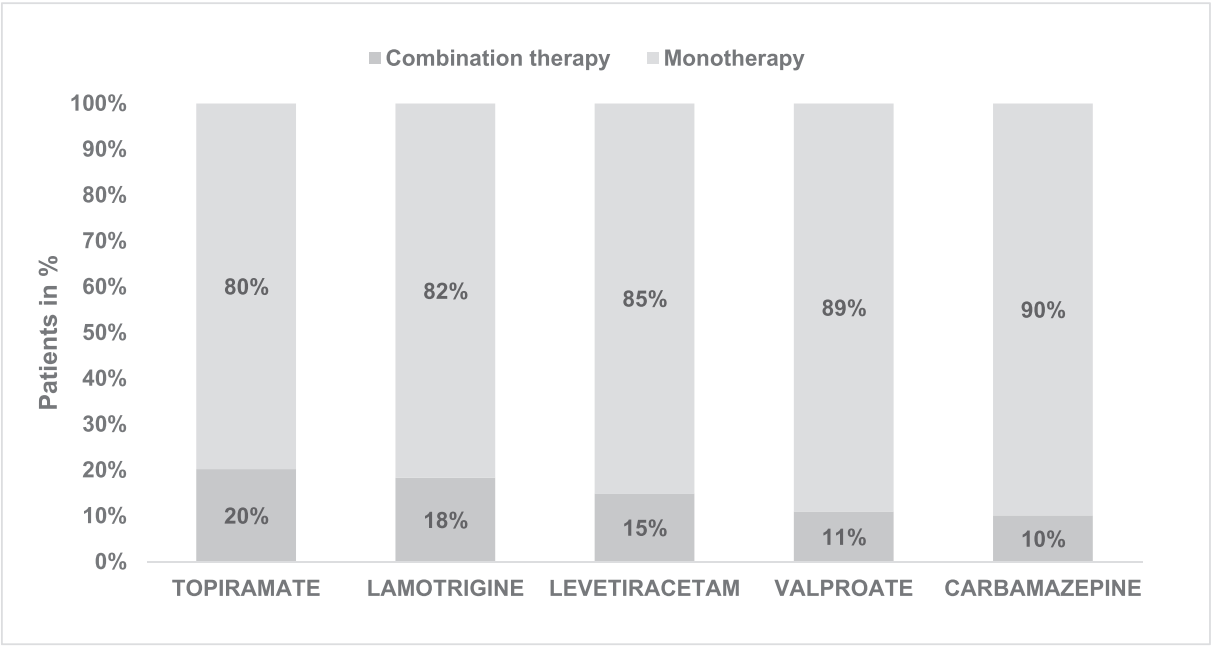

Fig. 2. Prescription patterns of AEDs in patients with epilepsy in Kazakhstan in 2018. Note: Total N was 57,959, with 4822 patients (8.3%) receiving at least two AEDs at the same time.

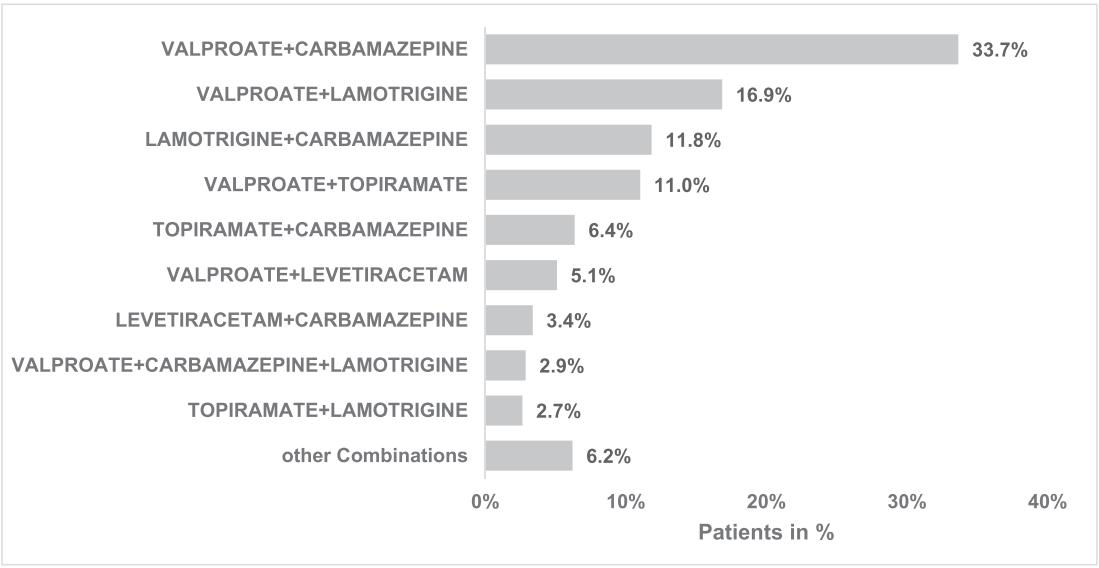

Fig. 3. Most frequent combination therapies of AEDs in patients with epilepsy in Kazakhstan in 2018. Note: This analysis was restricted to patients with epilepsy receiving combinations of AEDs.

action such as valproate (i.e., gamma-aminobutyric acid [GABA] enhancer) and carbamazepine (i.e., sodium channel blocker) is interesting in terms of their synergic effects and reduced risk of additional side effects. Finally, we observed substantial differences in AED prescription patterns in patients with epilepsy between Kazakhstan and Germany. Valproate (21.3%) and carbamazepine (13.3%) were prescribed in a smaller proportion of patients in Germany, whereas lacosamide (6.0%) and oxcarbazepine (4.0%) were more common there. This may be explained by differences in the availability of AEDs between Kazakh and German pharmaceutical markets, as well as by differences in the management and the treatment of epilepsy between these countries.

4.3. Strengths and limitations

The two major strengths of this study are the large sample size and the use of a pharmacy database. However, the findings of this study should be interpreted in light of several limitations. First, we had access to the data of individuals benefitting from free healthcare only, and thus the results may not be generalizable to the whole country. Second, we had no information on prescribers (e.g., general practitioner, neurologist), although such data may have led to a better understanding of the prescription patterns of AEDs. Third, this was a retrospective study, and missing data may have biased the subsequent descriptive analyses. Finally, it is difficult to explain the high proportion of young women receiving valproate. It is not clear if physicians in Kazakhstan base their prescription decisions on European therapy guidelines and if country specific guidelines are similar to the European guidelines.

Table 2
Comparison of prescription patterns of the most frequent AEDs between Kazakhstan and Germany in 2018.

Molecule	Prevalence among patients with epilepsy in Kazakhstan (N = 57,959)	Prevalence among patients with epilepsy in Germany (N = 15,476)
Levetiracetam	7.2	37.6
Lamotrigine	16.8	23.2
Valproate	54.6	21.3
Carbamazepine	49.3	13.3
Lacosamide	Not available	6.0
Oxcarbazepine	<0.01	4.0
Topiramate	9.9	3.0

Note: All drugs that were prescribed in more than 3% of patients in Germany are displayed. In Germany in 2018, 15,476 patients with epilepsy received at least one prescription for AEDs.

5. Conclusions

Patients with epilepsy were frequently prescribed valproate, carbamazepine, and lamotrigine in Kazakhstan in 2018. Further research is needed to gain a better understanding of the prescription of valproate in women with epilepsy of childbearing age. Based on the study results, there is still a need to improve epilepsy care in Kazakhstan.

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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