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Prescription Patterns of Antiepileptic Drugs and Co-prescribed Medications in Patients with Epilepsy in Kazakhstan (2021-2023)

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Abstract

Background/Objectives: Epilepsy is a major neurological disorder associated with significant comorbidity and treatment challenges. In low- and middle-income countries, access to newer antiseizure medications remains limited, and prescription patterns often rely on older agents. This study aimed to characterize national prescribing patterns of antiepileptic drugs (AEDs), assess monotherapy versus polytherapy use, and examine comorbid medication profiles among patients with epilepsy in Kazakhstan from 2021 to 2023. **Methods**: We conducted a retrospective observational study using de-identified electronic health record data from the Unified National Electronic Health System of Kazakhstan. All patients with an ICD-10 diagnosis of epilepsy (G40) and at least one AED prescription during 2021–2023 were included. Prescription frequencies, therapy type, and chronic polytherapy levels were analyzed. Non-AED medications were categorized using the WHO ATC classification, and the most common comorbid drugs were identified. Associations between therapy type, age, and comorbidity status were determined. **Results**: A total of 54,274 patients were identified (median age 42 years; IQR 31–57). Monotherapy predominated: 61.7% remained on monotherapy, 18.5% remained on polytherapy, and 19.8% had mixed exposure. Overall, 12.3% escalated from monotherapy to polytherapy and 11.3% de-escalated from polytherapy to monotherapy. Carbamazepine and valproic acid were most frequently prescribed (64.3% and 45.6% of patients, respectively). Lamotrigine (20.4%) and levetiracetam (15.2%) showed year-on-year increases, topiramate was stable (8.8%), and oxcarbazepine remained infrequent but rose from a low baseline (2.4%). Among those with chronic medication data (n=15,752), nervous-system drugs were common (70.1%), led by psycholeptics (49.7%); frequently dispensed agents included chlorpromazine (n=5,991), clozapine (n=1,875), and risperidone (n=1,642). Cardiovascular agents were recorded in 37.2% (acetylsalicylic acid n=4,056; atorvastatin n=2,235), and diabetes drugs in 12.1% (metformin n=1,430). **Conclusions**: AED prescribing in Kazakhstan is dominated by older broad-spectrum agents, with increasing uptake of lamotrigine and levetiracetam. High monotherapy rates align with guideline-concordant care, whereas escalation and de-escalation patterns reflect the dynamic management of refractory disease. The frequent use of psychotropic and cardiometabolic medicines highlights the need for integrated, multidisciplinary care and ongoing surveillance of prescribing to optimize safety and effectiveness.

Keywords: epilepsy; anticonvulsants; drug prescriptions; drug therapy; combination; comorbidity

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1. Introduction

Epilepsy is a common neurological disorder that affects approximately 1% of the global population [1]. The prevalence rates of epilepsy vary across the world, with approximately 80% of all patients with epilepsy residing in low- and middle-income countries (LMICs) [1]. In particular, several of the Central Asian countries experience a gradual increase in incidence, prevalence, and mortality rates, as most of them belong to low-, lower-middle-, or upper-middle-income categories [2]. Among them, Kazakhstan shows growing incidence and prevalence rates from 26.15 in 2014 to 88.80 in 2020 and 26.06 in 2014 to 73.10 in 2020 per 100,000 people, respectively [3].

Despite this burden, a substantial treatment gap persists worldwide, particularly in low- and middle-income countries (LMICs), where up to 75% of people with epilepsy remain untreated compared with 10% in high-income countries [4]. This gap is driven by limited drug availability, healthcare infrastructure challenges, lack of specialists, and stigma [5]. Reliance on older antiepileptic drugs (AEDs), poor adherence, and delays in diagnosis often hinder seizure control, even when treatment is available [6]. Addressing this gap requires integrating epilepsy care into primary health systems and improving access to effective, affordable medications.

According to current guidelines, the optimal management of epilepsy relies on AEDs to prevent recurrent seizures [7]. Monotherapy is typically preferred as the first-line treatment because approximately 60%–70% of patients can achieve long-term seizure remission with a single AED [8–10]. Clinical guidelines recommend monotherapy whenever possible due to lower risks of adverse effects and drug interactions [11–13]. Polytherapy, defined as the prescription of two or more AEDs concurrently, is usually reserved for refractory epilepsy cases where seizures are not controlled by one medication or in specific scenarios such as multiple seizure types [14]. Balancing efficacy and side effects is crucial; while polytherapy may improve seizure control in difficult cases, it also increases treatment complexity and the risk of toxicity [15].

AED prescription patterns have evolved over time with the introduction of newer medications. Traditional “first-generation” AEDs, such as valproic acid and carbamazepine, remain widely used, especially in LMICs, due to their broad effectiveness and familiarity [16–19]. Over the past two decades, newer AEDs (e.g., levetiracetam, lamotrigine, and topiramate) have gained popularity due to their improved safety profiles and specific indications [20–22]. Monitoring trends in the use of AEDs is important to ensure alignment with current evidence and guidelines [23]. For example, concerns about valproate’s teratogenicity have prompted initiatives to limit its use in women of childbearing age [24,25]. Changes in prescribing trends can also reflect the dissemination of new guidelines, the availability of new drugs, and the influence of healthcare policies [26].

Comorbidities represent another critical aspect of epilepsy care. Patients with epilepsy often have co-occurring psychiatric and somatic conditions. Approximately one-third of individuals with epilepsy have at least one psychiatric disorder, such as depression or anxiety, which is several-fold higher than that of the general population [27–29]. Epidemiologic data also show elevated rates of cardiovascular and metabolic conditions among patients with epilepsy [30–33]. These comorbidities can complicate treatment: clinicians must consider drug–drug interactions and, when possible, choose AEDs that also benefit or at least do not worsen comorbid conditions [34,35]. Conversely, the presence of multiple comorbidities often leads to polypharmacy, increasing the risk of side effects and adherence challenges [36].

In this study, we analyzed prescription data from 2021 to 2023 to characterize current AED prescribing patterns and treatment strategies among patients with epilepsy in Kazakhstan. We provide a comprehensive overview of the distribution of AEDs and their combinations, the relative use of monotherapy versus polytherapy and the prevalence of comorbid conditions together with associated non-AED medications. Variations by epilepsy subtype (ICD-10 codes) and region were also explored. This study aims to identify gaps in care and opportunities for improving epilepsy management by benchmarking these findings against prior data and international norms. Ultimately, this research is intended to inform clinicians, policymakers, and public health officials working to

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optimize therapy for epilepsy—a condition that imposes a significant burden not only through seizures but also through its frequent comorbidities and psychosocial implications.

2. Materials and Methods

Study Population and Data Sources

We conducted a retrospective observational study using de-identified electronic health record data from the Unified National Electronic Health System of Kazakhstan for the years 2021–2023. This database captures outpatient prescription dispensations and associated diagnoses across all regions of the country. We included adults (≥18 years) with a documented diagnosis of epilepsy (ICD-10 code G40 or any G40.x subgroup), who received at least one AED prescription during the study period. Patients older than 18 years were included. The final cohort included 54,274 unique patients.

This study was conducted under a broader protocol for secondary analysis of de-identified health data, with ethical approval obtained from the Local Bioethics Committee of the Hospital, as documented in Protocol No. 4, dated December 20, 2024 and in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective use of anonymized data.

Definitions

Patients were considered present in a given calendar year if they had at least one AED dispensed in that year. Cohort entry was defined as the first observed year and exit as the absence of subsequent dispensations, allowing dynamic participation across 2021–2023. Each dispensation event (including refills) was counted as a prescription for descriptive totals. At cohort entry, we tabulated ICD-10 G40.x categories and summarized them for descriptive purposes. All AEDs were identified and summarized at the ingredient level to capture patient-level prevalence and prescription counts. All non-AED comedications were mapped to WHO ATC anatomical main groups (A–V). For these non-AED drugs, we reported the proportion of patients with at least one prescription in each group and highlighted commonly used classes and subclasses (e.g., antithrombotics B01, lipid-modifying agents C10, diabetes drugs A10), as well as leading individual agents to illustrate practice patterns. Within each year, therapy status was inferred from overlapping exposure windows constructed from dispensation dates and recorded coverage: monotherapy was defined as only one AED active at a time, whereas polytherapy required overlap of two or more AEDs. Sequential use of multiple AEDs without overlap was classified as monotherapy. Across 2021–2023, patients were categorized as always monotherapy, always polytherapy, or mixed (at least one year of each). Between adjacent years (from 2021 to 2022 and fro**m** 2022 to 2023), changes were labeled as intensified (from mono- to polytherapy), deintensified (from poly- to monotherapy), switched (both mono- and polytherapy states across the two years without a single net direction), or stable. These definitions were used to derive transition counts and proportions. In a predefined chronic-polypharmacy subset (n=15,752) with complete chronic-use metadata, we enumerated concurrent drug counts by category (AEDs, somatic, psychiatric). The same overlap logic was applied to construct distributions (2, 3, 4, …, ≥10 agents) and to quantify overlaps across categories. For regional analyses, patients were assigned to one of 17 administrative regions or to one of three major cities (Almaty, Astana, Shymkent) based on residence recorded in the national system. We compared therapy patterns (monotherapy share), age, and comedication burden between the pooled major-city group and other regions.

Statistical Analysis

Continuous variables were summarized as median (IQR), and categorical variables as counts (percentages). Group comparisons were performed using Pearson's χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. For year-to-year descriptive trends, we did not test across calendar years because of within-person correlation; regression analyses were conducted at the patient-level. Factors associated with escalation to polytherapy were examined with

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a multivariable logistic regression estimating the odds of switching from monotherapy to polytherapy at any time during 2021–2023. Covariates included age (per 5-year increment), comorbidity burden (count of distinct chronic non-AED drugs per patient), and ICD-10 category at the first A**ED** (reference: G40.8). We reported odds ratios with 95% confidence intervals and two-sided p-values; $p<0.05$ was considered significant. All analyses were performed in R (version 4.3.0) using the following packages: dplyr, tidyr, stringr, purrr, forcats, lubridate, ggplot2, scales, broom, and knitr, (with base stats functions for χ^2, Wilcoxon tests, Fisher's test, and logistic regression).

3. Results

Patient Characteristics

A total of 54,274 patients with epilepsy were identified between 2021 and 2023. The median age was 42 years (IQR 31–57). The most frequently recorded ICD-10 codes were G40.8 "other epilepsy" (24.9%), G40 "epilepsy" not otherwise specified (21.4%), G40.2 localization-related symptomatic with complex partial seizures (20.6%), and G40.3 generalized idiopathic epilepsies (19.6). Less frequent codes were G40.1 simple partial (10.2%), G40.4 other generalized (6.3%), and G40.9 unspecified (8.1%); G40.5–G40.7 were rare (each ≤0.8%). Because more than one code could be assigned over time, categories were not mutually exclusive (Table 1). Regarding treatment level across observed years, 61.7% were consistently on monotherapy (n=33,471), 18.5% consistently on polytherapy (n=10,052), and 19.8% had mixed exposure (n=10,751). At least one prescription for the following AEDs was recorded: carbamazepine in 64.3% (n=34,894), valproic acid 45.6% (n=24,766), lamotrigine 20.4% (n=11,070), levetiracetam 15.2% (n=8,263), topiramate 8.8% (n=4,794), and oxcarbazepine 2.4% (n=1,327).

Table 1. General characteristics of studied patients with epilepsy and current treatment of epilepsy (N=54,274).

	Value
Age, median (IQR)	42 (31-57)
ICD, number of patients (%)	
G40	11608 (21.4%)
G40.1	5509 (10.2%)
G40.2	11170 (20.6%)
G40.3	10632 (19.6%)
G40.4	3392 (6.3%)
G40.5	421 (0.8%)
G40.6	62 (0.1%)
G40.7	40 (0.07%)
G40.8	13544 (24.9%)
G40.9	4408 (8.1%)
Level of therapy, number of patients (%)	
Monotherapy	33471 (61.7%)
Polytherapy	10052 (18.5%)
Switched from monotherapy to polytherapy	6664 (12.3%)
Switched from polytherapy to monotherapy	6135 (11.3%)
Prescribed AEDs, number of patients (%)	
Carbamazepine	34894 (64.3%)
Valproic acid	24766 (45.6%)
Lamotrigine	11070 (20.4%)
Levetiracetam	8263 (15.2%)
Topiramate	4794 (8.8%)
Oxcarbazepine	1327 (2.4%)

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AEDs Prescription Patterns

Across 2021–2023, the six most frequently used AEDs accounted for 651,377 prescriptions: carbamazepine (n=259,202), valproic acid (n=177,605), lamotrigine (n=100,180), levetiracetam (n=74,455), topiramate (n=33,023), and oxcarbazepine (n=6,912) (Figure 2). Year-specific totals were characterized by a dip and subsequent increase for carbamazepine (92,607 in 2021; 57,023 in 2022; 109,572 in 2023) and steady increases for valproic acid (54,531; 57,594; 65,480), lamotrigine (from 28,147 to 29,327 to 42,706), and levetiracetam (from 16,636 to 20,847 to 36,972). Topiramate remained stable (10,822; 10,645; 11,556). Oxcarbazepine increased from a low baseline (872; 2,158; 3,882).

Two-drug regimens accounted for 68.9% of observed combinations (n=15,214), most frequently carbamazepine and valproic acid (n=6,773; 12.5% of the cohort), lamotrigine and valproic acid (n=1,834; 3.4%), carbamazepine and levetiracetam (n=1,612; 3.0%), carbamazepine and lamotrigine (n=1,542; 2.8%), levetiracetam and valproic acid (n=924; 1.7%), carbamazepine and topiramate (n=676; 1.2%), and topiramate and valproic acid (n=627; 1.2%) (Figure 1). Three-drug regimens accounted for 23.7% of combinations (n=5,244)—dominated by carbamazepine - lamotrigine - valproic acid (n=1,666; 3.1% of the cohort), carbamazepine - levetiracetam - valproic acid (n=1,027; 1.9%), and carbamazepine - topiramate - valproic acid (n=700; 1.3%). Regimens with ≥4 drugs were uncommon overall (four drugs n=1,397; five n=228; six n=7; ~3.0% of the cohort).

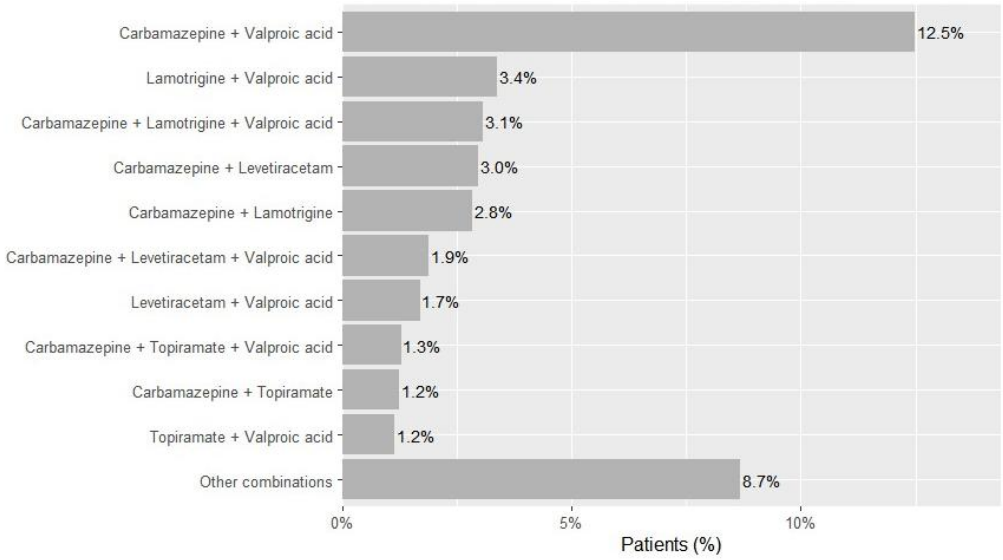

Figure 1. Most frequent AEDs combinations in patients with epilepsy in Kazakhstan across 2021-2023.

Therapy level varied by year: monotherapy accounted for 70.1% of regimens in 2021, 65.7% in 2022, and 72.4% in 2023, with polytherapy showing the reciprocal pattern (29.9%, 34.3%, 27.6%). Across adjacent years, intensification (mono to poly) occurred in 10.4% from 2021 to 2022 and 5.2% from 2022 to 2023; de-intensification (poly to mono) in 7.4% and 6.8%; and bidirectional switching in 3.2% and 2.1%, respectively. In total, 71.7% (n=38,924) maintained the same therapy level during observed years, while 28.3% (n=15,350) changed at least once (Figure 2). Cohort entry and exit were dynamic: 41,364 entered in 2021; 7,904 were new in 2022 (14.6% of the cohort) and 5,006 in 2023 (9.2%); 8,279 ceased to appear in 2022 (15.3%) and 17,464 in 2023 (32.2%).

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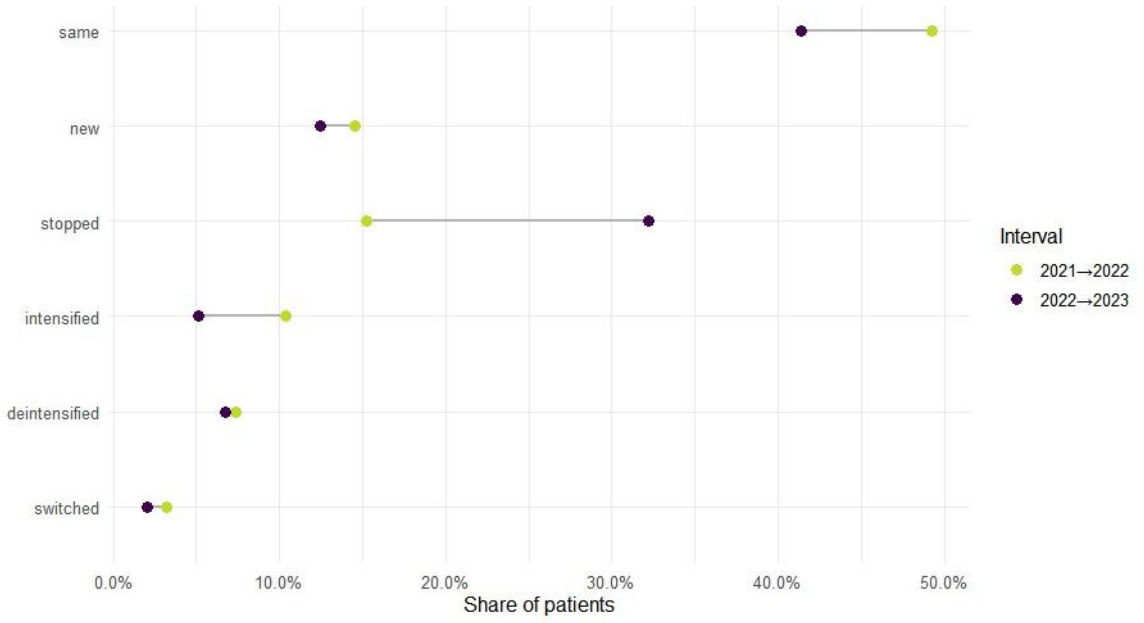

Figure 2. AED treatment regimen changes across years.

Mono-to-Polytherapy Transitions Among AED-Treated Patients

Overall, 6,664 of 54,274 patients (12.3%) were observed to escalate from monotherapy to polytherapy during 2021–2023. Median age at first AED was similar in non-switchers versus switchers (39 [28–54] versus 39 [29–52]; p<0.01), yet an inverse association with age was estimated in the adjusted model: OR 0.98 (95% CI 0.98–0.99) per 5 years; p<0.01. Comorbidity burden (distinct non-AED chronic drugs per patient) was not associated with switching: OR 1.00 (0.98–1.01); p=0.82. Using G40.8 as the reference ICD code at the first AED prescription, higher odds of switching were observed for G40.3: OR 1.15 (1.06–1.24); p<0.01. Lower odds were found for G40.2: OR 0.85 (0.78–0.92); p<0.01 and for G40.1: OR 0.89 (0.81–0.99); p=0.03. Other categories showed no significant associations (Table 2).

Table 2. Factors associated with switching from monotherapy to polytherapy (N = 6,664).

	OR (95% CI)	p-value
Age	0.98 (0.98 - 0.99)	<0.01*
Comorbid drugs	1.00 (0.97 – 1.01)	0.82
ICD		
G40.2	0.85 (0.78 – 0.92)	<0.01*
G40.3	1.15 (1.06 – 1.24)	<0.01*
G40.0	0.99 (0.91 – 1.08)	0.84
G40.1	0.89 (0.8 – 0.99)	0.03*
G40.9	0.97 (0.87 – 1.08)	0.6
G40.4	1.00 (0.88 – 1.12)	0.94
G40	1.01 (0.87 – 1.16)	0.91
G40.5	0.71 (0.48 – 1.00)	0.06
G40.6	0.82 (0.31 – 1.75)	0.64
G40.7	0.85 (0.25 – 2.13)	0.75

* Note: * = p<0.05.

Chronic Polytherapy Patterns

Among patients with chronic medication data (n=15,752), treatment intensity was skewed toward lower counts (Table 3). For AEDs, two-drug regimens were most frequent (26.6%), followed

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by three-drug courses (10.2%); higher AED counts were rare. Somatic and psychiatric drug classes showed longer right tails: while two to three agents predominated, a minority received five or more. Considering all chronic drugs, most patients used two to four agents (two drugs 22.4%, three drugs 13.3%, four drugs 8.4%), whereas only small fractions used nine or more. Co-prescribing was common: 62.9% received both AEDs and somatic drugs (n=9,909), 50.8% received both AEDs and psychiatric drugs (n=8,000), and 13.9% received agents from all three classes (n=2,197).

Table 3. Number of drugs used chronically by patients with epilepsy.

Chronic Polytherapy Level	AEDs	Somatic Drugs	Psychiatric Drugs	Total
2 drugs	4,192 (26.6%)	2,087 (13.2%)	1,846 (11.7%)	3,529 (22.4%)
3 drugs	1,612 (10.2%)	1,227 (7.8%)	974 (6.2%)	2,095 (13.3%)
4 drugs	448 (2.8%)	796 (5.1%)	479 (3.0%)	1,320 (8.4%)
5 drugs	73 (0.5%)	512 (3.3%)	309 (2.0%)	904 (5.7%)
6 drugs	2 (0.01%)	329 (2.1%)	140 (0.9%)	613 (3.9%)
7 drugs	0	222 (1.4%)	72 (0.5%)	389 (2.5%)
8 drugs	0	151 (1.0%)	25 (0.2%)	219 (1.4%)
9 drugs	0	106 (0.7%)	1 (0.006%)	146 (0.9%)
10 drugs	0	82 (0.5%)	0	97 (0.6%)
10+ drugs	0	129 (0.8%)	0	155 (1.0%)

By ATC, 70.1% received nervous-system drugs (N), led by psycholeptics (N05, 49.7%). Frequently dispensed agents included chlorpromazine (n=5,991), clozapine (n=1,875), levomepromazine (n=1,831), risperidone (n=1,642), trihexyphenidyl (n=1,704), and amitriptyline (n=1,259). Cardiovascular drugs were used by 37.2% (notably lipid-modifying agents, 14.2%—atorvastatin n=2,235—and beta-blockers, 7.9%—bisoprolol n=1,159), and 27.8% received agents for blood and blood-forming organs (antithrombotics 27.5%—acetylsalicylic acid n=4,056). Alimentary and metabolism drugs were used by 15.1% (diabetes drugs 12.1%—metformin n=1,430). Other classes included endocrine (8.3%; thyroid therapy 6.6%), respiratory (4.9%), anti-infectives (4.1%), and antineoplastic/immunomodulating (4.0%) (Table 4).

Table 4. Medications used by the patients with epilepsy (n = 15752) during 2021-2023 as categorized by the Anatomical Therapeutic Chemical (ATC) classification system.

Medications classified according to ATC	N (%) of patients
Alimentary tract and metabolism (A)	2373 (15.1%)
Drugs used in diabetes (A10)	1911 (12.1%)
Drugs for acid related disorders (A02)	345 (2.2%)
Antidiarrheals, intestinal anti-inflammatories/anti-infectives (A07)	53 (0.3%)
Laxatives (A06)	36 (0.2%)

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Drugs for functional gastrointestinal disorders (A03)	22 (0.1%)
Digestives, incl. enzymes (A09)	5 (0.03%)
Other alimentary tract and metabolism products (A16)	1 (0.006%)
Blood and blood forming organs (B)	4371 (27.8%)
Antithrombotic agents (B01)	4332 (27.5%)
Antianemic preparations (B03)	24 (0.15%)
Antihemorrhagics (B02)	15 (0.1%)
Cardiovascular system (C)	5859 (37.2%)
Lipid modifying agents (C10)	2235 (14.2%)
Beta blocking agents (C07)	1247 (7.9%)
Diuretics (C03)	892 (5.7%)
Cardiac therapy (C01)	780 (4.9%)
Calcium channel blockers (C08)	390 (2.5%)
Agents acting on the renin-angiotensin system (C09)	315 (1.9%)
Genito-urinary system and sex hormones (G)	87 (0.5%)
Other gynecologicals (G02)	87 (0.5%)
Systemic hormonal preparations, excl. sex hormones and insulins (H)	1303 (8.3%)
Thyroid therapy (H03)	1032 (6.6%)
Corticosteroids for systemic use (H02)	260 (1.7%)
Pituitary and hypothalamic hormones and analogues (H01)	11 (0.07%)
Antiinfectives for systemic use (J)	648 (4.1%)
Antibacterials for systemic use (J01)	601 (3.8%)
Antivirals for systemic use (J05)	47 (0.3%)
Antineoplastic and immunomodulating agents (L)	633 (4.02%)
Antineoplastic agents (L01)	482 (3.1%)
Endocrine therapy (L02)	64 (0.4%)
Immunosuppressants (L04)	48 (0.3%)
Immunostimulants (L03)	39 (0.25%)
Musculo-skeletal system (M)	342 (2.2%)
Anti-inflammatory and antirheumatic products (M01)	303 (1.9%)
Drugs for treatment of bone diseases (M05)	34 (0.2%)
Muscle relaxants (M03)	5 (0.03%)
Nervous system (N)	11044 (70.1%)
Psycholeptics (N05)	7831 (49.7%)
Anti-parkinson drugs (N04)	1713 (10.9%)
Psychoanaleptics (N06)	1259 (7.9%)
Analgesics (N02)	236 (1.5%)
Other nervous system drugs (N07)	5 (0.03%)
Antiparasitic products, insecticides and repellents (P)	29 (0.18%)
Antiprotozoals (P01)	29 (0.18%)
Respiratory system (R)	780 (4.9%)
Drugs for obstructive airway diseases (R03)	780 (4.9%)
Various (V)	2 (0.01%)
All other therapeutic products (V03)	2 (0.01%)

Regional Patterns in Treatment and Comorbidity

Patients were recorded in 17 regions and 3 major cities (Figure 3). The largest shares were from Turkistan Region (n=6,519; 11.7%) and Almaty city (n=5,875; 10.6%), followed by Almaty Region

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(n=3,846; 6.9%), Zhambyl (n=3,665; 6.6%), Shymkent (n=3,229; 5.8%), Aktobe (n=3,146; 5.7%), Karaganda (n=3,056; 5.5%), and Astana (n=2,961; 5.3%). Smaller contributions included Ulytau (n=633; 1.1%) and North Kazakhstan (n=1,231; 2.2%). Prescription volume broadly mirrored patient distributions, with higher absolute numbers in urban centers (for example, Almaty city 133,941 total prescriptions; Astana 53,344), and substantial AED dispensing alongside comorbidity treatment in high-volume regions (for example, Karaganda 61,172 total; Aktobe 54,646; Almaty Region 56,489; Zhambyl 59,102). Regions with smaller populations had correspondingly fewer prescriptions (for example, Ulytau 5,763; North Kazakhstan 13,178).

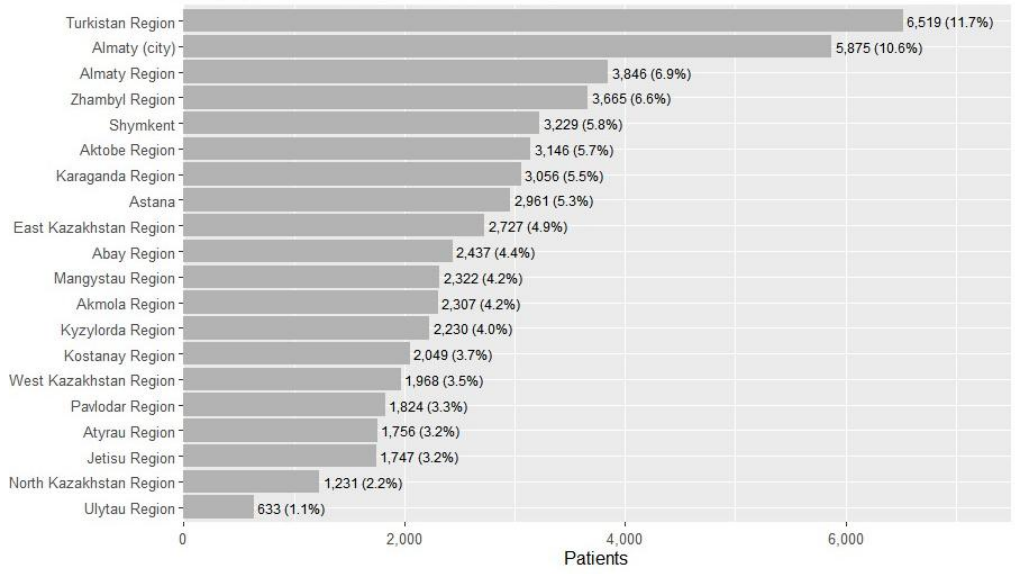

Figure 3. Patients with epilepsy receiving AEDs by regions (2021-2023).

Across 2021–2023, 21.8% of patients resided in the three main cities (Almaty, Astana, Shymkent; n=11,952) and 78.2% in other regions (n=42,875). Monotherapy was more frequent in the main cities (63.1%) than in other regions (58.5%), while polytherapy was less common (36.9% versus 41.5%; both p<0.01). Median age was slightly higher in cities (41 years [IQR 29–56]) than elsewhere (40 [29–54]; p<0.01). Comorbidity burden was modestly higher in cities (median 2 [1–4]) versus other regions (2 [1–3]; p<0.01) (Table 5).

Table 5. Patient characteristics and AED treatment profile in three main cities of Kazakhstan (Almaty, Astana, Shymkent) versus other regions, 2021–2023.

	Almaty, Astana, Shymkent	Regions	p-value1
Patients (n; % of cohort)	11952 (21.8%)	42875 (78.2%)	NA
Polytherapy share	36.9% (4410/11952)	41.5% (17792/42875)	<0.01
Age, median [IQR] (years)	41 [29–56]	40 [29–54]	<0.01
Comorbid drugs per patient, median [IQR]	2 [1–4]	2 [1–3]	<0.01

[1]Wilcoxon rank-sum.

4. Discussion

In this nationwide analysis of 54,274 patients with epilepsy in Kazakhstan (2021–2023), we observed that monotherapy remains the dominant treatment approach. About 61.7% of patients were managed on a single AED, whereas 18.5% received chronic polytherapy with multiple AEDs. The

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remaining patients experienced changes in regimen intensity over time: 12.3% escalated from monotherapy to polytherapy, while 11.3% were de-escalated from polytherapy to monotherapy during the study period. These findings underscore that most patients can be maintained on one AED, consistent with clinical guidelines recommending monotherapy whenever possible [37]. Notably, our monotherapy rate (61.7%) is higher than that reported in a multicenter study from India (42.6% monotherapy) [38], but lower than findings from a nation-wide Norwegian prescription study reporting 82% monotherapy [39]. A higher monotherapy share can reflect effective seizure control in routine care and prudent step-up to combinations only when needed, but may also mirror constraints in drug availability. Clinically, prioritizing single-agent regimens supports adherence and reduces adverse effects [40].

Carbamazepine and valproic acid dominated prescribing, with carbamazepine recorded for 64.3% and valproate for 45.6% of patients. This pattern resembles findings from several LMICs where older AEDs remain first-line (Al Za'abi et al., 2013; Eshiet et al., 2020). At the same time, a gradual rise in lamotrigine and levetiracetam use suggests ongoing uptake of newer-generation agents with favorable interaction profiles (Hochbaum et al., 2022; Perucca, 2006; Sánchez Fernández et al., 2023). The transient dip in carbamazepine prescriptions—alongside a brief uptick in polytherapy—may indicate a year-specific supply or practice effect, after which earlier patterns resumed. Oxcarbazepine and other newer agents remained infrequently used, consistent with cost and availability barriers in resource-limited contexts (Hailemariam et al., 2023; Sengxeu et al., 2020; Singh et al., 2020).

Therapy dynamics were common: nearly one-third of patients changed intensity at least once across adjacent years. In adjusted analyses, older age was associated with lower odds of escalation (OR 0.98 per year), while ICD-10 category at first AED distinguished groups modestly (higher odds for G40.3; lower for G40.2 and G40.1). These signals are consistent with clinical heterogeneity in drug responsiveness and underscore the need for timely referral of patients with persistent seizures to specialist care for advanced pharmacologic options, surgical evaluation, or neuromodulation (Jehi et al., 2022; Kwan et al., 2010; Löscher et al., 2020).

Polypharmacy extended beyond antiseizure treatment. Among those with chronic medication data, two to three concurrent drugs were typical, but a meaningful minority received five or more, particularly for somatic and psychiatric conditions. Psycholeptics were prominent; chlorpromazine was the most frequently dispensed psychotropic, with clozapine also common. This pattern raises two concerns. First, use of sedating typical antipsychotics as sleep or behavioral agents—described in some post-Soviet settings—can inflate apparent "psychosis" treatment and expose patients to avoidable adverse effects (Kuzo et al., 2024; Mann & Marwaha, 2023; Sateia et al., 2017; Zajicek, 2019). Second, clozapine's dose-dependent seizure risk complicates co-management with AEDs and warrants close collaboration between psychiatry and neurology (Devinsky et al., 1991; Hatano et al., 2023; Varma et al., 2011; Wong & Delva, 2007). The high rate of trihexyphenidyl likely reflects management of extrapyramidal symptoms from older antipsychotics (Jilani et al., 2024; Vanegas-Arroyave et al., 2024).

Our study also sheds light on the burden of comorbid conditions in epilepsy and how it translates to polypharmacy. We found that approximately 29% of the patients were on treatment for at least one comorbidity, and these patients were more likely to require multiple AEDs. This aligns with the concept that epilepsy with comorbidities (particularly structural brain lesions or progressive diseases) tends to be more difficult to control. Comorbid conditions such as stroke, dementia, or neurodevelopmental disabilities often underlie more refractory epilepsies [41–43]. We observed a high prevalence of psychotropic medication use: nearly half of those with comorbidities were on antipsychotic or anxiolytic drugs. This proportion is higher than expected from epidemiological data that ~20–30% of people with epilepsy have affective or anxiety disorders and only a few percent have psychosis [44–46]. One explanation might be the use of low-dose typical antipsychotics (e.g., chlorpromazine or levomepromazine) for indications other than primary psychosis–for example, as sedatives for sleep or behavioral control [47,48]. Older antipsychotics are sometimes used off-label in some post-Soviet countries for their sedative effects [49,50]. The prominence of chlorpromazine as

 doi:10.20944/preprints202509.2587.v1

the most prescribed comedication is a striking finding; it suggests a practice pattern that may warrant re-examination, given the side effect profile of chlorpromazine and the availability of safer alternatives for anxiety or insomnia [47,48,51]. On the other hand, the frequent use of clozapine (an atypical antipsychotic) raises concern because clozapine can cause seizures dose-dependently – managing patients on both clozapine and AEDs can be challenging and requires collaboration between psychiatry and neurology (perhaps these are patients with comorbid schizophrenia or schizoaffective disorders) [52–55]. The high use of trihexyphenidyl corroborates the fact that many patients were on older antipsychotics and developed extrapyramidal symptoms [56,57].

The presence of cardiovascular/metabolic medications in one-third of comorbid patients is expected, given the age profile of epilepsy care and the high burden of hypertension, dyslipidemia, and diabetes reported among people with epilepsy [31,58–60]. Certain AEDs warrant particular coordination with primary care: enzyme-inducing AEDs such as carbamazepine, phenytoin, and phenobarbital are associated with higher LDL-cholesterol and triglycerides, and they can reduce the anticoagulant effect of warfarin and some direct oral anticoagulants; valproate is linked to clinically relevant weight gain and insulin resistance [61–69]. The finding that 24.5% of patients were on aspirin is compatible with a substantial burden of atherosclerotic or cerebrovascular disease in this population; in older adults, stroke is the most common cause of new-onset epilepsy, underscoring the need for multidisciplinary care that addresses secondary stroke prevention alongside seizure control [70,71]. These patients essentially require a multidisciplinary approach that addresses stroke prevention alongside seizures. Likewise, the proportions on diabetes drugs (12.1%) and statins (14.2%) reinforce the importance of integrating lifestyle and cardiometabolic risk management into epilepsy care and considering AED selection with metabolic and interaction profiles in mind [31,64,69]

We identified noteworthy regional disparities in treatment patterns. Monotherapy rates were higher in the major urban centers (Almaty, Astana, Shymkent) compared to more peripheral regions, whereas the overall comorbidity burden appeared greater in city patients. These differences likely reflect variations in healthcare access and patient case-mix between urban and rural areas. Urban centers host specialized neurology services and experienced epileptologists, which may facilitate optimal management—physicians in tertiary centers might be more adept at achieving seizure control with a single well-chosen drug, and have access to a broader range of AEDs, than practitioners in rural areas. Our data suggest that big-city patients were more often kept on monotherapy, consistent with the presence of specialist care adhering to best practices. In contrast, patients from rural regions may have had higher rates of polytherapy (and possibly undertreated or uncontrolled epilepsy), which could be due to later referrals or limited drug availability locally. This pattern aligns with the known treatment gap in epilepsy care in low-resource settings [72,73]. Prior research in Southern Kazakhstan found the prevalence of epilepsy to be almost 60% higher in rural areas than urban areas (4.95 vs 3.14 per 1000), which suggests that many rural patients historically did not receive optimal therapy or were not under active specialist follow-up [74]. Our finding that urban patients also carried a higher burden of comorbid illnesses (e.g., more on antithrombotics and statins in cities) could indicate that complex patients (such as elderly individuals with multiple conditions or those with stroke-related epilepsy) are preferentially managed in the city hospitals. Urban centers may thus see a concentration of both the most severe epilepsy cases and those with multiple health problems, leading to high comedication rates. This dual phenomenon—better adherence to monotherapy in cities, but also higher multimorbidity in city populations—highlights a challenge for healthcare planners. Efforts are needed to close the urban-rural gap by extending specialist training and telemedicine support to rural practitioners, ensuring that effective monotherapy is pursued whenever feasible even outside major hospitals. At the same time, resources in urban clinics must cater to the broader health needs of their patients, emphasizing multidisciplinary management (cardiology, endocrinology, psychiatry) alongside epilepsy care.

Our study's strengths include a large, population-based sample and linkage of pharmacy dispensing with diagnosis codes and concomitant medications, which supports external validity and

 doi:10.20944/preprints202509.2587.v1

richer clinical profiling [75]. Important limitations remain. Clinical outcomes (seizure frequency, severity, seizure freedom) and adherence cannot be inferred from dispensing alone; overlapping days' supply can misclassify brief switches as polytherapy, although this operationalization is standard in drug-utilization research (Hempenius et al., 2021; Pazzagli et al., 2022; Rasmussen et al., 2022; Steiner & Prochazka, 1997). ICD-based case identification may include miscoding or single seizures; combining epilepsy codes with repeated AED dispensings improves positive predictive value (Fonferko-Shadrach et al., 2017; Mbizvo et al., 2020; Reid et al., 2012). Comorbidity estimates based on medications are conservative and cannot distinguish multi-indication use (Mannion et al., 2020; Pratt et al., 2018).

In high-income health systems, use of carbamazepine and valproate has fallen while lamotrigine and levetiracetam have risen, as shown in national prescribing datasets [76,77]. By contrast, older, lower-cost agents remain prevalent in resource-constrained settings where availability and affordability shape treatment choices [78]. Ongoing surveillance of prescribing using individual-level dispensing data is therefore valuable for assessing concordance with evidence and detecting emerging signals [75]. Two examples illustrate the utility of such monitoring: (i) persistently high valproate use among women of childbearing potential should trigger targeted safety measures in light of dose-related teratogenic and neurodevelopmental risks [79,80], and (ii) a marked increase in polytherapy may reflect greater clinical complexity (i.e., more drug-resistant epilepsy) or suboptimal escalation in less severe cases, warranting audit against monotherapy-first principles [81].

5. Conclusions

In conclusion, this study provides a comprehensive overview of epilepsy management within a health system undergoing transition in the early 2020s. Concordance with established patterns—predominant monotherapy, continued use of older agents, and a substantial burden of comorbidities—supports the validity of the dataset and reinforces core principles of epilepsy care. At the same time, context-specific features—most notably the unusually frequent use of chlorpromazine—identify priorities for local audit and practice improvement. Sustaining robust seizure control while minimizing unnecessary polypharmacy and addressing broader health needs remains a central objective. Integrating care for psychiatric and medical comorbidities within epilepsy pathways is likely to enhance quality of life and may support better seizure outcomes, given the potential for conditions such as depression and diabetes to complicate management.

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Data Availability Statement: The data that support the findings of this study are available from the Republican Center for Electronic Health of the Ministry of Health of the Republic of Kazakhstan. Restrictions apply to the availability of these data; they were used under license for the current study and are not publicly available. Data may be obtained from one of the authors (A. Gaipov) upon reasonable request and with permission of the Ministry of Health of the Republic of Kazakhstan.

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Abbreviations

The following abbreviations are used in this manuscript:

AED(s)	Antiepileptic drug(s)
ICD-10	International Classification of Diseases, 10th Revision
WHO ATC	World Health Organization Anatomical Therapeutic Chemical classification
LMICs	Low- and middle-income countries
LDL	Low-density lipoprotein

References

1. Feigin, V.L.; Vos, T.; Nair, B.S.; Hay, S.I.; Abate, Y.H.; Magied, A.H.A.A.A.; ElHafeez, S.A.; Abdelkader, A.; Abdollahifar, M.-A.; Abdullahi, A.; et al. Global, Regional, and National Burden of Epilepsy, 1990–2021: A Systematic Analysis for the Global Burden of Disease Study 2021. *The Lancet Public Health* **2025**, *10*, e203–e227. https://doi.org/10.1016/S2468-2667(24)00302-5.
2. Kalinina, D.; Akhmedullin, R.; Muxunov, A.; Sarsenov, R.; Sarria-Santamera, A. Epidemiological Trends of Idiopathic Epilepsy in Central Asia: Insights from the Global Burden of Disease Study (1990–2021). *Seizure - European Journal of Epilepsy* **2025**, *131*, 233–239. https://doi.org/10.1016/j.seizure.2025.07.013.
3. Akhmedullin, R.; Kozhobekova, B.; Gusmanov, A.; Aimyshev, T.; Utebekov, Z.; Kyrgyzbay, G.; Shpekov, A.; Gaipov, A. Epilepsy Trends in Kazakhstan: A Retrospective Longitudinal Study Using Data from Unified National Electronic Health System 2014–2020. *Seizure: European Journal of Epilepsy* **2024**, *122*, 58–63. https://doi.org/10.1016/j.seizure.2024.09.022.
4. Meyer, A.-C.; Dua, T.; Ma, J.; Saxena, S.; Birbeck, G. Global Disparities in the Epilepsy Treatment Gap: A Systematic Review. *Bull. World Health Organ.* **2010**, *88*, 260–266. https://doi.org/10.2471/BLT.09.064147.
5. Mbuba, C.K.; Newton, C.R. Packages of Care for Epilepsy in Low- and Middle-Income Countries. *PLoS Med* **2009**, *6*, e1000162. https://doi.org/10.1371/journal.pmed.1000162.
6. WHO Epilepsy: A Public Health Imperative Available online: https://www.who.int/publications/i/item/epilepsy-a-public-health-imperative (accessed on 16 August 2025).
7. Nevitt, S.J.; Sudell, M.; Cividini, S.; Marson, A.G.; Smith, C.T. Antiepileptic Drug Monotherapy for Epilepsy: A Network Meta-analysis of Individual Participant Data - Nevitt, SJ - 2022 | Cochrane Library. **2022**.
8. Cockerell, O.C.; Sander, J.W. a. S.; Hart, Y.M.; Shorvon, S.D.; Johnson, A.L. Remission of Epilepsy: Results from the National General Practice Study of Epilepsy. *The Lancet* **1995**, *346*, 140–144. https://doi.org/10.5555/uri:pii:S0140673695912088.
9. Hauser, W.A.; Annegers, J.F.; Kurland, L.T. Incidence of Epilepsy and Unprovoked Seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* **1993**, *34*, 453–458. https://doi.org/10.1111/j.1528-1157.1993.tb02586.x.
10. Sander, J.W. The Use of Antiepileptic Drugs--Principles and Practice. *Epilepsia* **2004**, *45 Suppl 6*, 28–34. https://doi.org/10.1111/j.0013-9580.2004.455005.x.
11. Ko, D.Y. Epilepsy and Seizures Treatment & Management: Approach Considerations, Anticonvulsant Therapy, Anticonvulsants for Specific Seizure Types. **2022**.
12. Krumholz, A.; Wiebe, S.; Gronseth, G.S.; Gloss, D.S.; Sanchez, A.M.; Kabir, A.A.; Liferidge, A.T.; Martello, J.P.; Kanner, A.M.; Shinnar, S.; et al. Evidence-Based Guideline: Management of an Unprovoked First Seizure in Adults. *Neurology* **2015**, *84*, 1705–1713. https://doi.org/10.1212/WNL.0000000000001487.

 doi:10.20944/preprints202509.2587.v1

13. St. Louis, E. Minimizing AED Adverse Effects: Improving Quality of Life in the Interictal State in Epilepsy Care. *Curr Neuropharmacol* **2009**, *7*, 106–114. https://doi.org/10.2174/157015909788848857.
14. St. Louis, E.K. Truly "Rational" Polytherapy: Maximizing Efficacy and Minimizing Drug Interactions, Drug Load, and Adverse Effects. *Current Neuropharmacology* **2009**, *7*, 96–105. https://doi.org/10.2174/157015909788848929.
15. Li, C.; Wang, X.; Deng, M.; Luo, Q.; Yang, C.; Gu, Z.; Lin, S.; Luo, Y.; Chen, L.; Li, Y.; et al. Antiepileptic Drug Combinations for Epilepsy: Mechanisms, Clinical Strategies, and Future Prospects. *International Journal of Molecular Sciences* **2025**, *26*, 4035. https://doi.org/10.3390/ijms26094035.
16. Jacob, L.; Kerimbaeva, Z.; Kalyapin, A.; Kostev, K. Prescription Patterns of Antiepileptic Drugs in Kazakhstan in 2018: A Retrospective Study of 57,959 Patients. *Epilepsy & Behavior* **2019**, *99*, 106445. https://doi.org/10.1016/j.yebeh.2019.106445.
17. Kang, K.W.; Lee, H.; Shin, J.-Y.; Moon, H.-J.; Lee, S.-Y. Trends in Prescribing of Antiseizure Medications in South Korea: Real-World Evidence for Treated Patients With Epilepsy. *Journal of Clinical Neurology* **2022**, *18*, 179–193. https://doi.org/10.3988/jcn.2022.18.2.179.
18. Liang, C.-Y.; Chiang, K.-L.; Hsieh, L.-P.; Chien, L.-N. Prescription Patterns and Dosages of Antiepileptic Drugs in Prevalent Patients with Epilepsy in Taiwan: A Nationwide Retrospective Cross-Sectional Study. *Epilepsy & Behavior* **2022**, *126*, 108450. https://doi.org/10.1016/j.yebeh.2021.108450.
19. Singh, G.; Goraya, J. The Medical Management of Epilepsy in Low- and Middle-Income Countries. In *Epilepsy: A Global Approach*; Krishnamoorthy, E.S., Shorvon, S.D., Schachter, S.C., Eds.; Cambridge University Press: Cambridge, 2017; pp. 105–109 ISBN 978-1-107-03537-9.
20. Chappell, B.; Crawford, P. An Audit of Lamotrigine, Levetiracetam and Topiramate Usage for Epilepsy in a District General Hospital. *Seizure* **2005**, *14*, 422–428. https://doi.org/10.1016/j.seizure.2005.07.005.
21. French, J.A.; Gazzola, D.M. New Generation Antiepileptic Drugs: What Do They Offer in Terms of Improved Tolerability and Safety? *Ther Adv Drug Saf* **2011**, *2*, 141–158. https://doi.org/10.1177/2042098611411127.
22. Marson, A.; Burnside, G.; Appleton, R.; Smith, D.; Leach, J.P.; Sills, G.; Tudur-Smith, C.; Plumpton, C.; Hughes, D.A.; Williamson, P.; et al. The SANAD II Study of the Effectiveness and Cost-Effectiveness of Levetiracetam, Zonisamide, or Lamotrigine for Newly Diagnosed Focal Epilepsy: An Open-Label, Non-Inferiority, Multicentre, Phase 4, Randomised Controlled Trial. *Lancet* **2021**, *397*, 1363–1374. https://doi.org/10.1016/S0140-6736(21)00247-6.
23. Hoeltzenbein, M.; Slimi, S.; Fietz, A.-K.; Dathe, K.; Schaefer, C. Trends in Use of Antiseizure Medication and Treatment Pattern during the First Trimester in the German Embryotox Cohort. *Sci Rep* **2024**, *14*, 30585. https://doi.org/10.1038/s41598-024-83060-9.
24. Kim, H.; Faught, E.; Thurman, D.J.; Fishman, J.; Kalilani, L. Antiepileptic Drug Treatment Patterns in Women of Childbearing Age With Epilepsy. *JAMA Neurology* **2019**, *76*, 783–790. https://doi.org/10.1001/jamaneurol.2019.0447.
25. Tomson, T.; Battino, D. Teratogenic Effects of Antiepileptic Drugs. *Lancet Neurol* **2012**, *11*, 803–813. https://doi.org/10.1016/S1474-4422(12)70103-5.
26. Heger, K.; Skipsfjord, J.; Kiselev, Y.; Burns, M.L.; Aaberg, K.M.; Johannessen, S.I.; Skurtveit, S.; Johannessen Landmark, C. Changes in the Use of Antiseizure Medications in Children and Adolescents in Norway, 2009–2018. *Epilepsy Research* **2022**, *181*, 106872. https://doi.org/10.1016/j.eplepsyres.2022.106872.
27. Kanner, A.M.; Shankar, R.; Margraf, N.G.; Schmitz, B.; Ben-Menachem, E.; Sander, J.W. Mood Disorders in Adults with Epilepsy: A Review of Unrecognized Facts and Common Misconceptions. *Annals of General Psychiatry* **2024**, *23*, 11. https://doi.org/10.1186/s12991-024-00493-2.
28. Kwon, O.-Y.; Park, S.-P. Depression and Anxiety in People with Epilepsy. *Journal of Clinical Neurology* **2014**, *10*, 175–188. https://doi.org/10.3988/jcn.2014.10.3.175.
29. Rai, D.; Kerr, M.P.; McManus, S.; Jordanova, V.; Lewis, G.; Brugha, T.S. Epilepsy and Psychiatric Comorbidity: A Nationally Representative Population-Based Study. *Epilepsia* **2012**, *53*, 1095–1103. https://doi.org/10.1111/j.1528-1167.2012.03500.x.

 doi:10.20944/preprints202509.2587.v1

30. Bruun, E.; Virta, L.J.; Kälviäinen, R.; Keränen, T. Co-Morbidity and Clinically Significant Interactions between Antiepileptic Drugs and Other Drugs in Elderly Patients with Newly Diagnosed Epilepsy. *Epilepsy Behav* **2017**, *73*, 71–76. https://doi.org/10.1016/j.yebeh.2017.05.022.
31. Gaertner, M.L.; Mintzer, S.; DeGiorgio, C.M. Increased Cardiovascular Risk in Epilepsy. *Front Neurol* **2024**, *15*, 1339276. https://doi.org/10.3389/fneur.2024.1339276.
32. Loureiro Fialho, G.; Miotto, R.; Tatsch Cavagnollo, M.; Murilo Melo, H.; Wolf, P.; Walz, R.; Lin, K. The Epileptic Heart: Cardiac Comorbidities and Complications of Epilepsy. Atrial and Ventricular Structure and Function by Echocardiography in Individuals with Epilepsy – From Clinical Implications to Individualized Assessment. *Epilepsy & Behavior Reports* **2024**, *26*, 100668. https://doi.org/10.1016/j.ebr.2024.100668.
33. Wang, J.; Huang, P.; Yu, Q.; Lu, J.; Liu, P.; Yang, Y.; Feng, Z.; Cai, J.; Yang, G.; Yuan, H.; et al. Epilepsy and Long-Term Risk of Arrhythmias. *Eur Heart J* **2023**, *44*, 3374–3382. https://doi.org/10.1093/eurheartj/ehad523.
34. Bosak, M.; Słowik, A.; Iwańska, A.; Lipińska, M.; Turaj, W. Co-Medication and Potential Drug Interactions among Patients with Epilepsy. *Seizure* **2019**, *66*, 47–52. https://doi.org/10.1016/j.seizure.2019.01.014.
35. Seo, J.-G.; Cho, Y.W.; Kim, K.T.; Kim, D.W.; Yang, K.I.; Lee, S.-T.; Byun, J.-I.; No, Y.J.; Kang, K.W.; Kim, D.; et al. Pharmacological Treatment of Epilepsy in Elderly Patients. *Journal of Clinical Neurology* **2020**, *16*, 556–561. https://doi.org/10.3988/jcn.2020.16.4.556.
36. Tadesse, T.A.; Belayneh, A.; Aynalem, M.W.; Yifru, Y.M.; Amare, F.; Beyene, D.A. Potentially Inappropriate Prescribing in Elderly Patients with Epilepsy at Two Referral Hospitals in Ethiopia. *Front. Med.* **2024**, *11*. https://doi.org/10.3389/fmed.2024.1403546.
37. NICE Overview | Epilepsies in Children, Young People and Adults | Guidance | NICE Available online: https://www.nice.org.uk/guidance/ng217?utm_source=chatgpt.com (accessed on 18 August 2025).
38. Mehndiratta, M.M.; Kukkuta Sarma, G.R.; Tripathi, M.; Ravat, S.; Gopinath, S.; Babu, S.; Mishra, U.K. A Multicenter, Cross-Sectional, Observational Study on Epilepsy and Its Management Practices in India. *Neurology India* **2022**, *70*, 2031. https://doi.org/10.4103/0028-3886.359162.
39. Johannessen Landmark, C.; Larsson, P.G.; Rytter, E.; Johannessen, S.I. Antiepileptic Drugs in Epilepsy and Other Disorders--a Population-Based Study of Prescriptions. *Epilepsy Res* **2009**, *87*, 31–39. https://doi.org/10.1016/j.eplepsyres.2009.07.005.
40. Andrew, T.; Milinis, K.; Baker, G.; Wieshmann, U. Self Reported Adverse Effects of Mono and Polytherapy for Epilepsy. *Seizure - European Journal of Epilepsy* **2012**, *21*, 610–613. https://doi.org/10.1016/j.seizure.2012.06.013.
41. Abokrysha, N.T.; Taha, N.; Shamloul, R.; Elsayed, S.; Osama, W.; Hatem, G. Clinical, Radiological and Electrophysiological Predictors for Drug-Resistant Epilepsy. *Egypt J Neurol Psychiatr Neurosurg* **2023**, *59*, 44. https://doi.org/10.1186/s41983-023-00647-1.
42. Perucca, E.; Perucca, P.; White, H.S.; Wirrell, E.C. Drug Resistance in Epilepsy. *The Lancet Neurology* **2023**, *22*, 723–734. https://doi.org/10.1016/S1474-4422(23)00151-5.
43. Xue-Ping, W.; Hai-Jiao, W.; Li-Na, Z.; Xu, D.; Ling, L. Risk Factors for Drug-Resistant Epilepsy: A Systematic Review and Meta-Analysis. *Medicine* **2019**, *98*, e16402. https://doi.org/10.1097/MD.0000000000016402.
44. Clancy, M.J.; Clarke, M.C.; Connor, D.J.; Cannon, M.; Cotter, D.R. The Prevalence of Psychosis in Epilepsy; a Systematic Review and Meta-Analysis. *BMC Psychiatry* **2014**, *14*, 75. https://doi.org/10.1186/1471-244X-14-75.
45. Fiest, K.M.; Dykeman, J.; Patten, S.B.; Wiebe, S.; Kaplan, G.G.; Maxwell, C.J.; Bulloch, A.G.M.; Jette, N. Depression in Epilepsy. *Neurology* **2013**, *80*, 590–599. https://doi.org/10.1212/WNL.0b013e31827b1ae0.
46. Scott, A.J.; Sharpe, L.; Hunt, C.; Gandy, M. Anxiety and Depressive Disorders in People with Epilepsy: A Meta-Analysis. *Epilepsia* **2017**, *58*, 973–982. https://doi.org/10.1111/epi.13769.
47. Mann, S.K.; Marwaha, R. Chlorpromazine. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2023.
48. Sateia, M.J.; Buysse, D.J.; Krystal, A.D.; Neubauer, D.N.; Heald, J.L. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine* **2017**, *13*, 307–349. https://doi.org/10.5664/jcsm.6470.

 doi:10.20944/preprints202509.2587.v1

49. Kuzo, N.; Blyzniuk, B.; Chumakov, E.; Seifritz, E.; de Leon, J.; Schoretsanitis, G. Clozapine Research Standards in Former USSR States: A Systematic Review of Quality Issues with Recommendations for Future Harmonization with Modern Research Standards. *Schizophrenia Research* **2024**, *268*, 48–52. https://doi.org/10.1016/j.schres.2023.10.040.
50. Zajicek, B. The Psychopharmacological Revolution in the USSR: Schizophrenia Treatment and the Thaw in Soviet Psychiatry, 1954–64. *Med Hist* **2019**, *63*, 249–269. https://doi.org/10.1017/mdh.2019.26.
51. DeGeorge, K.C.; Grover, M.; Streeter, G.S. Generalized Anxiety Disorder and Panic Disorder in Adults. *afp* **2022**, *106*, 157–164.
52. Devinsky, O.; Honigfeld, G.; Patin, J. Clozapine-related Seizures. *Neurology* **1991**, *41*, 369–369. https://doi.org/10.1212/WNL.41.3.369.
53. Hatano, M.; Yamada, K.; Matsuzaki, H.; Yokoi, R.; Saito, T.; Yamada, S. Analysis of Clozapine-Induced Seizures Using the Japanese Adverse Drug Event Report Database. *PLOS ONE* **2023**, *18*, e0287122. https://doi.org/10.1371/journal.pone.0287122.
54. Varma, S.; Bishara, D.; Besag, F.M.C.; Taylor, D. Clozapine-Related EEG Changes and Seizures: Dose and Plasma-Level Relationships. *Ther Adv Psychopharmacol* **2011**, *1*, 47–66. https://doi.org/10.1177/2045125311405566.
55. Wong, J.; Delva, N. Clozapine-Induced Seizures: Recognition and Treatment. *Can J Psychiatry* **2007**, *52*, 457–463. https://doi.org/10.1177/070674370705200708.
56. Jilani, T.N.; Sabir, S.; Patel, P.; Sharma, S. Trihexyphenidyl. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.
57. Vanegas-Arroyave, N.; Caroff, S.N.; Citrome, L.; Crasta, J.; McIntyre, R.S.; Meyer, J.M.; Patel, A.; Smith, J.M.; Farahmand, K.; Manahan, R.; et al. An Evidence-Based Update on Anticholinergic Use for Drug-Induced Movement Disorders. *CNS Drugs* **2024**, *38*, 239–254. https://doi.org/10.1007/s40263-024-01078-z.
58. Galiyeva, D.; Gusmanov, A.; Sakko, Y.; Issanov, A.; Atageldiyeva, K.; Kadyrzhanuly, K.; Nurpeissova, A.; Rakhimzhanova, M.; Durmanova, A.; Sarria-Santamera, A.; et al. Epidemiology of Type 1 and Type 2 Diabetes Mellitus in Kazakhstan: Data from Unified National Electronic Health System 2014–2019. *BMC Endocrine Disorders* **2022**, *22*, 275. https://doi.org/10.1186/s12902-022-01200-6.
59. Vivanco-Hidalgo, R.M.; Gomez, A.; Moreira, A.; Díez, L.; Elosua, R.; Roquer, J. Prevalence of Cardiovascular Risk Factors in People with Epilepsy. *Brain Behav* **2016**, *7*, e00618. https://doi.org/10.1002/brb3.618.
60. Yerdessov, S.; Kadyrzhanuly, K.; Sakko, Y.; Gusmanov, A.; Zhakhina, G.; Galiyeva, D.; Bekbossynova, M.; Salustri, A.; Gaipov, A. Epidemiology of Arterial Hypertension in Kazakhstan: Data from Unified Nationwide Electronic Healthcare System 2014–2019. *J Cardiovasc Dev Dis* **2022**, *9*, 52. https://doi.org/10.3390/jcdd9020052.
61. Clark, N.P.; Hoang, K.; Delate, T.; Horn, J.R.; Witt, D.M. Warfarin Interaction With Hepatic Cytochrome P-450 Enzyme-Inducing Anticonvulsants. *Clin Appl Thromb Hemost* **2018**, *24*, 172–178. https://doi.org/10.1177/1076029616687849.
62. Galgani, A.; Palleria, C.; Iannone, L.F.; De Sarro, G.; Giorgi, F.S.; Maschio, M.; Russo, E. Pharmacokinetic Interactions of Clinical Interest Between Direct Oral Anticoagulants and Antiepileptic Drugs. *Front. Neurol.* **2018**, *9*. https://doi.org/10.3389/fneur.2018.01067.
63. Mar, P.L.; Gopinathannair, R.; Gengler, B.E.; Chung, M.K.; Perez, A.; Dukes, J.; Ezekowitz, M.D.; Lakkireddy, D.; Lip, G.Y.H.; Miletello, M.; et al. Drug Interactions Affecting Oral Anticoagulant Use. *Circulation: Arrhythmia and Electrophysiology* **2022**, *15*, e007956. https://doi.org/10.1161/CIRCEP.121.007956.
64. Mintzer, S.; Maio, V.; Foley, K. Use of Antiepileptic Drugs and Lipid-Lowering Agents in The United States. *Epilepsy Behav* **2014**, *34*, 105–108. https://doi.org/10.1016/j.yebeh.2014.03.008.
65. Mintzer, S.; Yi, M.; Hegarty, S.; Maio, V.; Keith, S. Hyperlipidemia in Patients Newly Treated with Anticonvulsants: A Population Study. *Epilepsia* **2020**, *61*, 259–266. https://doi.org/10.1111/epi.16420.
66. Sarangi, S.C.; Pattnaik, S.S.; Dash, Y.; Tripathi, M.; Velpandian, T. Is There Any Concern of Insulin Resistance and Metabolic Dysfunctions with Antiseizure Medications? A Prospective Comparative Study of Valproate vs. Levetiracetam. *Seizure: European Journal of Epilepsy* **2024**, *121*, 123–132. https://doi.org/10.1016/j.seizure.2024.08.003.

 doi:10.20944/preprints202509.2587.v1

67. Sidhu, H.S.; Srinivas, R.; Sadhotra, A. Evaluate the Effects of Long-Term Valproic Acid Treatment on Metabolic Profiles in Newly Diagnosed or Untreated Female Epileptic Patients: A Prospective Study. *Seizure* **2017**, *48*, 15–21. https://doi.org/10.1016/j.seizure.2017.03.007.
68. Verrotti, A.; D'Egidio, C.; Mohn, A.; Coppola, G.; Chiarelli, F. Weight Gain Following Treatment with Valproic Acid: Pathogenetic Mechanisms and Clinical Implications. *Obes Rev* **2011**, *12*, e32-43. https://doi.org/10.1111/j.1467-789X.2010.00800.x.
69. Yamamoto, Y.; Terada, K.; Takahashi, Y.; Imai, K.; Kagawa, Y.; Inoue, Y. Influence of Antiepileptic Drugs on Serum Lipid Levels in Adult Epilepsy Patients. *Epilepsy Res* **2016**, *127*, 101–106. https://doi.org/10.1016/j.eplepsyres.2016.08.027.
70. Galovic, M.; Ferreira-Atuesta, C.; Abraira, L.; Döhler, N.; Sinka, L.; Brigo, F.; Bentes, C.; Zelano, J.; Koepp, M.J. Seizures and Epilepsy After Stroke: Epidemiology, Biomarkers and Management. *Drugs Aging* **2021**, *38*, 285–299. https://doi.org/10.1007/s40266-021-00837-7.
71. Liu, S.; Yu, W.; Lü, Y. The Causes of New-Onset Epilepsy and Seizures in the Elderly. *Neuropsychiatr Dis Treat* **2016**, *12*, 1425–1434. https://doi.org/10.2147/NDT.S107905.
72. Pellinen, J. Treatment Gaps in Epilepsy. *Front. Epidemiol.* **2022**, *2*. https://doi.org/10.3389/fepid.2022.976039.
73. Singh, B.; Mahajan, N.; Singh, G.; Sander, J.W. Temporal Trends in the Epilepsy Treatment Gap in Low- and Low-Middle-Income Countries: A Meta-Analysis. *Journal of the Neurological Sciences* **2022**, *434*, 120174. https://doi.org/10.1016/j.jns.2022.120174.
74. Guekht, A.; Zharkinbekova, N.; Shpak, A.; Hauser, W.A. Epilepsy and Treatment Gap in Urban and Rural Areas of the Southern Kazakhstan in Adults. *Epilepsy Behav* **2017**, *67*, 98–104. https://doi.org/10.1016/j.yebeh.2016.11.028.
75. Rasmussen, L.; Wettermark, B.; Steinke, D.; Pottegård, A. Core Concepts in Pharmacoepidemiology: Measures of Drug Utilization Based on Individual-level Drug Dispensing Data. *Pharmacoepidemiol Drug Saf* **2022**, *31*, 1015–1026. https://doi.org/10.1002/pds.5490.
76. Hochbaum, M.; Kienitz, R.; Rosenow, F.; Schulz, J.; Habermehl, L.; Langenbruch, L.; Kovac, S.; Knake, S.; von Podewils, F.; von Brauchitsch, S.; et al. Trends in Antiseizure Medication Prescription Patterns among All Adults, Women, and Older Adults with Epilepsy: A German Longitudinal Analysis from 2008 to 2020. *Epilepsy Behav* **2022**, *130*, 108666. https://doi.org/10.1016/j.yebeh.2022.108666.
77. Powell, G.; Logan, J.; Kiri, V.; Borghs, S. Trends in Antiepileptic Drug Treatment and Effectiveness in Clinical Practice in England from 2003 to 2016: A Retrospective Cohort Study Using Electronic Medical Records. *BMJ Open* **2019**, *9*, e032551. https://doi.org/10.1136/bmjopen-2019-032551.
78. Cameron, A.; Bansal, A.; Dua, T.; Hill, S.R.; Moshe, S.L.; Mantel-Teeuwisse, A.K.; Saxena, S. Mapping the Availability, Price, and Affordability of Antiepileptic Drugs in 46 Countries. *Epilepsia* **2012**, *53*, 962–969. https://doi.org/10.1111/j.1528-1167.2012.03446.x.
79. Meador, K.J.; Baker, G.A.; Browning, N.; Cohen, M.J.; Bromley, R.L.; Clayton-Smith, J.; Kalayjian, L.A.; Kanner, A.; Liporace, J.D.; Pennell, P.B.; et al. Fetal Antiepileptic Drug Exposure and Cognitive Outcomes at Age 6 Years (NEAD Study): A Prospective Observational Study. *Lancet Neurol* **2013**, *12*, 244–252. https://doi.org/10.1016/S1474-4422(12)70323-X.
80. Tomson, T.; Battino, D.; Bonizzoni, E.; Craig, J.; Lindhout, D.; Perucca, E.; Sabers, A.; Thomas, S.V.; Vajda, F.; For the EURAP Study Group Dose-Dependent Teratogenicity of Valproate in Mono- and Polytherapy. *Neurology* **2015**, *85*, 866–872. https://doi.org/10.1212/WNL.0000000000001772.
81. Kwan, P.; Arzimanoglou, A.; Berg, A.T.; Brodie, M.J.; Allen Hauser, W.; Mathern, G.; Moshé, S.L.; Perucca, E.; Wiebe, S.; French, J. Definition of Drug Resistant Epilepsy: Consensus Proposal by the Ad Hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* **2010**, *51*, 1069–1077. https://doi.org/10.1111/j.1528-1167.2009.02397.x.