JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/18978

The Impact of Antiepileptic Therapy on Anesthetic Requirements and Postoperative Pain in Patients with Pharmacoresistant Focal Epilepsy: a Retrospective Study

Mukhit Dossov[1], Azhar Zhailauova[2], Nazira Bekenova[3], Alisher Aitkalyev[3], Serik Seitenov[4]

[1]Anesthesiology and ICU Department, Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan
[2]Anesthesiology and ICU Residency Department, Nazarbayev University School of Medicine, Astana, Kazakhstan
[3]Department of Science, Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan
[4]Deputy head of the Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan

Received: 2026-01-31.
Accepted: 2026-07-20.

J Clin Med Kaz 2026; 23(4): 4-13

Corresponding author:
Mukhit Dossov.
E-mail: dossovmukhit@gmail.com.
ORCID: 0009-0000-3291-362X.

ABSTRACT

Background: Patients with pharmacoresistant focal epilepsy (PRE) are exposed to long-term antiepileptic drug (AED) therapy, which may influence anesthetic pharmacology and postoperative pain. However, evidence regarding the perioperative effects of chronic AED treatment remains scarce. The study aims to investigate the association of AED regimen, epilepsy duration, anesthetic consumption, and surgery with postoperative pain in patients with pharmacoresistant focal epilepsy.

Methods: The retrospective cohort study included 92 participants with pharmacoresistant focal epilepsy who underwent neurosurgical intervention between 2019 and 2024. Patients were stratified according to AED regimen into carbamazepine monotherapy (n=27), carbamazepine plus levetiracetam (n=44), and other AED combinations (n=21). Intraoperative anesthetic consumption, postoperative visual analogue scale (VAS) pain scores, analgesic requirements, and perioperative outcomes were compared. Predictors of postoperative pain were evaluated using multivariable logistic regression analysis.

Results: Patients receiving combination AED therapy had significantly longer epilepsy duration than those receiving carbamazepine monotherapy (median 16–18 vs. 8 years, $p<0.01$). Intraoperative consumption of fentanyl, propofol, sevoflurane, and neuromuscular blocking agents did not differ among treatment groups (all $p>0.05$). Postoperative pain occurred in 58.7% of patients, with similar VAS trajectories, analgesic requirements, and time to first analgesic request across groups. Surgery type was not associated with postoperative pain in either univariate or multivariable analyses. Multivariable logistic regression demonstrated no independent association between postoperative pain and AED regimen, intraoperative fentanyl dose, sex, or surgical procedure (all $p>0.05$). Sensitivity analysis limited to patients receiving carbamazepine or levetiracetam as the primary AED yielded consistent results, although levetiracetam showed a non-significant trend toward lower odds of postoperative pain compared with carbamazepine (adjusted OR 0.47, 95% CI 0.19–1.18).

Conclusions: Long-term AED regimen, epilepsy duration, and surgery type were not independently associated with anesthetic requirements or early postoperative pain in patients undergoing surgery for pharmacoresistant focal

epilepsy. Standardized perioperative anesthesia and postoperative analgesia appear to provide effective pain control regardless of chronic AED therapy. Larger prospective multicenter studies are needed to confirm these findings and evaluate the perioperative effects of individual AEDs.

Keywords: pharmacoresistant focal epilepsy; antiepileptic drugs; carbamazepine; levetiracetam; postoperative pain; anesthesia; epilepsy surgery; neurosurgery.

Introduction

Epilepsy is a neurological condition affecting approximately 70 million people worldwide, with a prevalence of 4 to 10 cases per 1,000 individuals [1,2]. Despite the ongoing development of various antiepileptic drugs (AEDs), drug resistance remains a significant issue. About one-third of epilepsy patients experience pharmacoresistant epilepsy (PRE) [3,4]. The most common type linked to treatment resistance is focal epilepsy, which represents over half of all cases [4]. Focal PRE refers to resistance to two or more AEDs and is often associated with a long disease duration. Some PRE patients are considered candidates for surgical intervention [5].

Over the last decade, epilepsy surgery has advanced with improvements in neuroimaging, high-resolution structural and functional mapping, intraoperative neuronavigation, and minimally invasive approaches. Nonetheless, challenges persist in personalized perioperative management, including optimizing anesthesia, maintaining hemodynamic stability, and managing antiepileptic drug interactions [1,6]. When a patient with pharmacoresistant epilepsy opts for surgery, care transitions from a neurologist-epileptologist to a multidisciplinary team that includes anesthesiologists and other specialists [6,7]. Long-term use of antiepileptic drugs in these patients alters neurological networks, affecting cognitive function and anesthetic response during surgery [6,8]. These changes might indicate that there is individual variability in how patients respond to anesthetic and analgesic drugs, including differences in pharmacokinetics and pharmacodynamics, the potential for drug interactions, and variations in postoperative pain levels [9].

The current range of antiepileptic drugs includes both microsomal enzyme inducers like carbamazepine and agents with minimal drug interactions such as levetiracetam. Cytochrome P 450 inducers accelerate the metabolism of opioids and certain anesthetic agents, thereby increasing intraoperative needs and reducing the effectiveness of analgesics and anesthetics [10]. Data on how antiepileptic drugs affect the minimum alveolar concentration (MAC) of inhalational anesthetics are limited [11]. Drugs with a low potential for interactions, such as levetiracetam, are associated with fewer early postoperative complications like seizures, agitation, and delayed recovery, especially in neurosurgical patients [12]. In non- neurosurgical populations, these drugs show a potential opioid- sparing effect; however, evidence in focal pharmacoresistant epilepsy remains limited [12]. Combination therapy may pose risks of adverse interactions and cumulative side effects such as dizziness, drowsiness, and ataxia, which can worsen during the perioperative period [13]. Postoperative pain syndrome (PPS) is also a key consideration during perioperative management of patients undergoing epilepsy or brain tumor surgery [14]. Neurosurgical procedures, especially craniotomies, are linked to significant postoperative pain, which if poorly controlled, can lead to complications like hypertension, tachycardia, increased intracranial pressure, agitation, sleep disturbances, delayed awakening, and longer ICU stays [14,15]. Inadequate pain management after craniotomy may increase stress responses, raise opioid use, and impair neurocognitive recovery [15] . Post- craniotomy pain peaks within the first 24–48 hours, with the worst intensity on the first postoperative day, correlating with higher analgesic use, delayed extubation, and longer recovery times [14]. Despite progress in epilepsy surgery and available anesthetic guidelines, research on how antiepileptic drugs, epilepsy duration, and their characteristics influence anesthetic and analgesic needs and postoperative pain levels is limited [7].

However, most existing research has concentrated on seizure prevention rather than personalized perioperative pain management. Many studies evaluate how effective various AED regimens, such as monotherapy versus combination therapy, are at stopping intraoperative and early postoperative seizures, especially in patients undergoing craniotomy or awake surgery [14,15,16]. Exploring this topic could help predict optimal anesthetic and opioid doses, personalize multimodal pain relief, decrease practice variability, and promote quicker recovery [17,18].

Considering all the above-mentioned, the aim of this study is to assess the impact of antiepileptic therapy characteristics and epilepsy duration on anesthetic consumption and the severity of postoperative pain in neurosurgical patients with focal pharmacoresistant epilepsy.

Methods

Study design and data selection

An investigation was conducted at the Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan using a retrospective cohort design. Between 2019 and 2024, a total of 130 patients who underwent surgical treatment for pharmacoresistant focal epilepsy were analyzed. After applying the inclusion and exclusion criteria, 38 patients were excluded for failing to meet the study criteria or for incomplete clinical data. The final analysis included 92 patients.

Inclusion criteria:

– age ≥18 years;

– confirmed diagnosis of pharmacoresistant focal epilepsy;

– undergone neurosurgical intervention with available medical documentation;

– completed perioperative period (up to 48 hours postoperatively).

Exclusion criteria:

– patients with generalized forms of epilepsy;

– patients with incomplete data on key variables;

– presence of severe comorbid somatic conditions (e.g., decompensated respiratory diseases, respiratory failure, end-stage cardiovascular failure, cancer, stage IV hepatic or renal failure);

– massive intraoperative bleeding; repeat surgeries.

As part of the retrospective analysis, anesthetic records of the patients included in the study were reviewed. Patients received general anesthesia according to the standardized protocol in the neurosurgery department.

Anesthesia induction started with intravenous propofol at 2 mg/kg and fentanyl at 2 μg/kg. Additional fentanyl was given every 20–30 minutes at 1–2 μg/kg, adjusted based on clinical signs of anesthesia depth. The adequacy of anesthesia was evaluated using clinical signs, hemodynamic responses (MAP, HR), and, when available, bispectral index (BIS) monitoring. Stable hemodynamics within ±20% of baseline and BIS values between 40 and 60 were considered indicative of sufficient anesthesia. Extra fentanyl doses were administered as needed to maintain these parameters.

Neuromuscular relaxation was achieved using rocuronium bromide at 0.6 mg/kg, followed by IV boluses of pipecuronium bromide at 0.01–0.02 mg/kg as needed. Anesthesia was maintained with sevoflurane at a MAC of 1.0–1.2%, with fresh gas flow set at 25–30% of the patient's minute ventilation, based on ideal body weight. The effectiveness of anesthesia was monitored using hemodynamic parameters, including invasive arterial blood pressure (IABP), heart rate (HR), and ECG. Perioperative respiratory status and oxygenation were assessed using arterial blood gases, capnography, and continuous pulse oximetry (SpO_2), with SpO_2 maintained≥93%. Intravenous fluids were administered per local protocol to support tissue perfusion. In cases of hemodynamic instability, defined as a mean arterial pressure (MAP) below 65 mmHg despite adequate fluid resuscitation, vasopressor support with titrated intravenous norepinephrine was initiated and continued until the target pressure was achieved.

Recorded Parameters for Analysis

Intraoperative parameters: total fentanyl dose (μg) administered during surgery; total volume of inhalational anesthetic (sevoflurane, mL); duration of anesthesia (minutes).

Postoperative pain assessment: visual analog scale (VAS) pain scores recorded at 2, 4, 6, 8, and 12 hours postoperatively; total dose of analgesics administered within the first 24 hours after surgery; and time to first request for analgesia. Postoperative analgesia comprised a three-step pain management protocol based on World Health Organization (WHO) guidelines [19]. The protocol was introduced into routine clinical practice alongside the standardized VAS scale. The analgesic protocol consisted of:

– Step 1: VAS 1–4 (mild pain) – nonsteroidal anti-inflammatory drugs (NSAIDs): intravenous Intrafen 800 mg or intramuscular ketoprofen 100 mg;

– Step 2: VAS 4–6 (moderate to severe pain) – synthetic opioids (tramadol 100 mg IM) and/or NSAIDs (Intrafen 800 mg IV or ketoprofen 100 mg IM);

– Step 3: VAS 7–10 (severe pain) – opioids (morphine 10 mg IM) and NSAIDs.

Additional recorded parameters: age, sex, body mass index (BMI); type of neurosurgical procedure; duration of epilepsy; duration of mechanical ventilation; Richmond Agitation-Sedation Scale (RASS) score [20]; length of stay in the intensive care unit (ICU); and presence of postoperative seizures.

Patients were stratified by antiepileptic drug therapy and divided into three groups: Group I, carbamazepine monotherapy; Group II, carbamazepine and levetiracetam combination; and Group III, other double antiepileptic drug combination.

Ethics

This study was conducted in accordance with an expanded protocol for the secondary analysis of de-identified medical data, with ethical approval from the Hospital's Local Bioethics Committee (Institutional Review Boards), as stated in Protocol No. 4, dated December 20, 2024, and in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analyses were conducted in SPSS Statistics (version 26) and JASP. Normality of variables was assessed with the Shapiro–Wilk test. For non-normally distributed data, the Mann–Whitney U test was used. Categorical variables were analyzed with the chi-squared test or Fisher's exact test, as appropriate. Multivariable logistic regression was performed to identify factors associated with postoperative pain. A p-value of <0.05 was considered statistically significant.

Results

Clinical and demographic characteristics of patients

92 patients who underwent surgery for pharmacoresistant focal epilepsy were included in the study. The mean age was 32.5 ± 8.0 years. Of the cohort, 54 (58.7%) were male, and 38 (41.3%) were female. The mean BMI value was 23.9 ± 4.7 kg/m². The distribution of surgical procedures was as follows: lobectomy – 75.0%, tumor resection – 10.9%, cortical dysplasia resection – 4.3%, cavernous hemangioma excision – 4.3%, arteriovenous malformation resection – 3.3%, ulegyria resection – 2.2%.

Carbamazepine was the most commonly used main antiepileptic medication (57/92, 62.0%) across all groups, followed by levetiracetam (32/92, 34.8%), valproic acid (2/92, 2.2%), and lamotrigine (1/92, 1.1%). Among patients on combination therapy (n = 65), additional antiepileptic medications were distributed as follows: carbamazepine (23/65, 35.4%), levetiracetam (21/65, 32.3%), lamotrigine (10/65, 15.4%), valproic acid (6/65, 9.2%), and topiramate (5/65, 7.7%). The results of patient stratification by antiepileptic therapy are presented in Table 1.

Table 1 Main AED and Additional AED by Treatment Group

Variable	Carbamazepine (n=27)	Carbamazepine + Levetiracetam (n=44)	Other AED (n=21)
Main AED			
Carbamazepine	27 (100.0%)	21 (47.7%)	9 (42.9%)
Levetiracetam	-	23 (52.3%)	9 (42.9%)
Valproic acid	-	-	2 (9.5%)
Lamotrigine	-	-	1 (4.8%)
Additional AED			
None	27 (100.0%)	-	-
Carbamazepine	-	23 (52.3%)	-
Levetiracetam	-	21 (47.7%)	-
Lamotrigine	-	-	10 (47.6%)
Valproic acid	-	-	6 (28.6%)
Topiramate	-	-	5 (23.8%)

Daily doses of the main antiepileptic medication varied across the groups as follows: 800 (400–800) mg/day in the carbamazepine group, 1000 (800–1625) mg/day in the carbamazepine + levetiracetam group, and 1000 (400–1500) mg/day in the other AED group. Pairwise group comparison with Bonferroni adjustment revealed a significantly lower antiepileptic medication dose in the carbamazepine group than in the carbamazepine + levetiracetam group ($p < 0.001$). There was no such difference between carbamazepine and other AED groups. Among patients on combination treatment, where an

Table 2 Comparison of the clinical and demographic characteristics among the groups

Parameter	Group I: Carbamazepine (N=27)	Group II: Carbamaze-pine + Levetiracetam (N=44)	Group III: Other AED Combinations (N=21)	p-value
Demographic and Clinical Data				
Age, years,	34.0 (27.5 – 38.5)	30.5 (26.0 – 35.25)	32 (29.0–38.0)	0.36[1-2] 0.43[2-3] 0.86[1-3]
Gender, n (%)				
Male	18 (66.7%)	24 (54.5%)	12 (57.1%)	0.594
Female	9 (33.3%)	20 (45.5%)	9 (42.9%)	
BMI (kg/m^2)	22.9 (22.11–28.46)	21.99 (19.11–26.08)	24.57 (20.2–28.2)	0.047[1-2*] 0.122-3 0.98[1-3]
Main Antiepileptic Drug (mg/day)	800 (400–800)	1000 (800–1625)	1000 (400–1500)	0.000021-2 0.1972-3 0.1121-3
Additional Antiepileptic Drug (mg/day)		1000 (400–1812.5)	350 (200–750)	0.00042-3
Epilepsy duration, years	8.0 (3.5–13.5)	16.0 (12.0–24.25)	18.0 (10.0–22.0)	0.0011-2 0.7412-3 0.0041-3
ASA	2 (2–2)	2 (2–2)	2 (2–2)	0.821-2 0.722-3 0.881-3
ASA I	0	1	0	
ASA II	26	41	2	
ASA III	1	2	1	
Anesthesia duration, min	555 (460–625)	555 (480–611.25)	555 (518.4–607.6)	0.821-2 0.512-3 0.651-3
Mechanical ventilation in ICU, min	65.0 (52.5–117.5)	100.0 (58.75–136.25)	60.0 (45.0–100.0)	0.271-2 0.0362-3* 0.261-3
RASS score	−2.0 (−3.0 to −2.0)	−2.5 (−3.0 to −2.0)	−2.0 (−3.0 to −2.0)	0.711-2 0.212-3 0.351-3
ICU stay, hours	15.0 (13.5–16.0)	14.0 (13.0–16.0)	14.0 (12.5–16.0)	0.771-2 0.522-3 0.361-3
Hospital stay, days	12.0 (8.0–14.5)	12.5 (10.0–16.0)	16.0 (14.0–19.0)	0.161-2 0.012-3 0.0021-3
Post-op seizures, incidence	1/27 (3.7%)	4/44(9.1%)	5/21 (23.8%)	0.6431-2** 0.1352-3** 0.0731-3**
Anesthetic Consumption Parameters				
Fentanyl dose, µg/kg	14.94 (12.90–18.18	15.56 (11.30–20.56	14.08 (11.24–17.54)	0.661-2 0.322-3 0.551-3
Propofol dose, mg,	132.0 (120.0–164.0)	131.0 (107.5–146.5)	142.0 (114.0–162.0)	0.121-2 0.422-3 0.521-3
Inhalational anesthetic, mL/hr	11.01 (8.45–14.09)	10.17 (8.19–12.49)	10.59 (8.81–14.29)	0.341-2 0.462-3 0.941-3
Pipecuronium, mg	12.0 (12.0–13.0) n=24	12.0 (8.0–16.0) n=35	10 (9.26–12.04) n=19	0.571-2 0.332-3 0.111-3
Rocuronium, mg	200 (175–200) n=3	150 (100–150) n=9	150 (100–200) n=2	0.221-2 1.002-3 1.001-3

*Me – median, (Q1–Q3) – interquartile range, p – Mann-Whitney test, *Bonferroni adjustment did not reveal a statistically significant difference. **Fisher's exact test. For gender distribution χ^2 ($\chi^2 = 1.04$, $p = 0.594$) was applied.*

additional antiepileptic medication is added, the dose of the additional antiepileptic medication was significantly higher in the carbamazepine + levetiracetam group, at 1000 (400–1812.5) mg/day, compared with the other AED group at 350 (200–750) mg/day ($p < 0.001$). Table 2 represents demographical, preoperative and intraoperative parameters across the groups.

The median age ranged from 30.5 to 34 years and did not differ significantly among the groups ($p > 0.05$). The gender distribution was also comparable across groups. The median BMI was higher in patients receiving combination therapy with other antiepileptic drugs than in those receiving carbamazepine monotherapy ($p = 0.047$), although after Bonferroni adjustment, the difference was not statistically significant ($p = 0.140$).

Disease duration varied significantly across groups ($p = 0.001$). The shortest duration of epilepsy was observed in patients receiving carbamazepine monotherapy, whereas those on combined therapy with levetiracetam and other AEDs had a significantly longer disease duration ($p = 0.011$), 8, 16, and 18 years, respectively. Mann–Whitney U tests with Bonferroni correction showed that the first group (carbamazepine group) had shorter disease duration than the second group (carbamazepine + levetiracetam; $p = 0.0021$) and the third group (other AED combinations; $p = 0.011$). The latter two groups did not differ in disease duration ($p > 0.05$). According to the ASA physical status classification system, most patients were classified as ASA class II ($p > 0.05$).

Anesthesia duration was comparable among the three groups, with values of 555 (460–625) min, 555 (480–611.25) min, and 555 (518.4–607.6) min, respectively ($p > 0.05$). Mechanical ventilation time tended to be higher in the carbamazepine + levetiracetam group, with the median 100.0 (60.0–135.0) min, in comparison to the carbamazepine group, with the median 65.0 (53.8–116.3) min, and the other AED group, with the median 60.0 (45.0–92.5) min. However, the difference among the groups did not reach statistical significance (p=0.07). Pairwise analysis demonstrated a statistically significant difference between the second and third groups ($p = 0.036$), but after Bonferroni correction, this significance was not maintained. The level of sedation, assessed using the RASS, was comparable across all groups ($p > 0.05$), suggesting similar arousal levels.

ICU stay did not differ significantly between the groups, with values of 15, 14, and 14 hours, respectively ($p > 0.05$). However, there was a difference in the overall hospital length of stay across the groups ($p = 0.0033$). The overall hospital stay of the first group comprised 12.0 (8.0–14.5) days, 12.5 (10.0–16.0) days for the second group, and 16.0 (14.0–19.0) days for the last group, illustrating the statistically significant discrepancy between the first two groups and the third one ($p = 0.006$ and $p = 0.026$, respectively). The incidence of postoperative seizures was relatively low across groups. Although the postoperative seizure rate was higher in the third group, 5/21 (23.8%), compared to the first group, 1/27 (3.7%), and the second group, 4/44 (9.1%), the difference did not reach statistical significance ($p = 0.074$).

Intraoperative consumption of the main anesthetics, analgesics, and neuromuscular blocking agents was comparable across the three groups. Induction dose of propofol was 132.0 (120.0–164.0) mg, 131.0 (107.5–146.5) mg, and 142.0 (114.0–162.0) mg in the carbamazepine, carbamazepine + levetiracetam, and other AED groups, respectively, demonstrating similar distribution ($p = 0.27$). Median values of inhalational anesthetic dose were 11.01 (8.45–14.09) mL/hour in the carbamazepine group, 10.17 (8.19–12.49) mL/hour in the carbamazepine + levetiracetam group, and 10.59 (8.81–14.29) mL/hour in the other AED group, illustrating also comparable consumption. Fentanyl doses adjusted for body weight showed no significant differences among the groups and comprised 14.94 (12.90–18.18), 15.56 (11.30–20.56), and 14.08 (11.24–17.54) mcg/kg, respectively. Due to prolonged surgery time, pipecuronium was preferred, and there was no difference in its consumption across groups ($p = 0.317$), although the median dose for the third group tended to be lower. Rocuronium was administered to a patient population with small sample sizes across three groups: n = 3, 9, and 2, respectively. The median dose of rocuronium in the carbamazepine group was the highest, at 200 (175–200) mg, while in the second and third groups it was 150 (100–150) mg and 150 (100–200) mg, respectively.

Postoperative pain assessment of patients

Postoperative pain was assessed using the VAS immediately after surgery, at 2, 4, 6, 8, and 12 hours postoperatively. The need for additional analgesia and the time to the first request for pain medication were also recorded. The results are presented in Table 3.

Postoperative pain was observed in more than half of the patient population across the groups, comprising 66.7%, 52.2%, and 66.7%, respectively. The differences in pain occurrence among the groups were not statistically significant ($p = 0.27$), indicating comparable pain severity in the early postoperative

Table 3 Assessment of postoperative pain syndrome across the treatment groups

Parameter	Group I: Carbamazepine, N=27	Group II: Carbamazepine + Levetiracetam, N=44	Group III: Other AED combinations, N=21	p-value
Patients with pain, n (%)	18 (66.7%)	22 (52.2%)	14 (66.7%)	0.27**
Postoperative pain (VAS)				
2 hours after surgery (points)	1.0 (0.0–2.5)	2.0 (1.0–3.0)	3.0 (2.0–4.0)	$0.098^{1\text{-}2}$ $0.18^{2\text{-}3}$ $0.028^{1\text{-}3*}$
4 hours after surgery (points)	3.0 (2.0–8.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	$0.42^{1\text{-}2}$ $0.92^{2\text{-}3}$ $0.60^{1\text{-}3}$
6 hours after surgery (points)	2.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (3.0–3.0)	$0.55^{1\text{-}2}$ $0.20^{2\text{-}3}$ $0.05^{1\text{-}3}$
8 hours after surgery (points)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	$0.70^{1\text{-}2}$ $0.15^{2\text{-}3}$ $0.29^{1\text{-}3}$
12 hours after surgery (points)	2.0 (0.5–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	$0.74^{1\text{-}2}$ $0.79^{2\text{-}3}$ $0.97^{1\text{-}3}$
Time of analgesic requirement after surgery (hours)	4.0 (4.0–4.0)	4.0 (2.25–5.75)	3.0 (2.0–4.75)	$0.99^{1\text{-}2}$ $0.24^{2\text{-}3}$ $0.17^{1\text{-}3}$
Frequency of additional analgesia after surgery with morphine, n (%)	8 (29.6%)	7 (15.9%)	7 (33.3%)	
Frequency of additional analgesia after surgery with tramadol, n (%)	4 (14.8%)	7 (15.9%)	4 (19.0%)	
Frequency of additional analgesia with NSAID after surgery, n (%)	6 (22.2%)	8 (18.2%)	3 (14.3%)	

*Me – median, (Q1–Q3) – interquartile range, p – Mann-Whitney test, ** Chi-square test.*

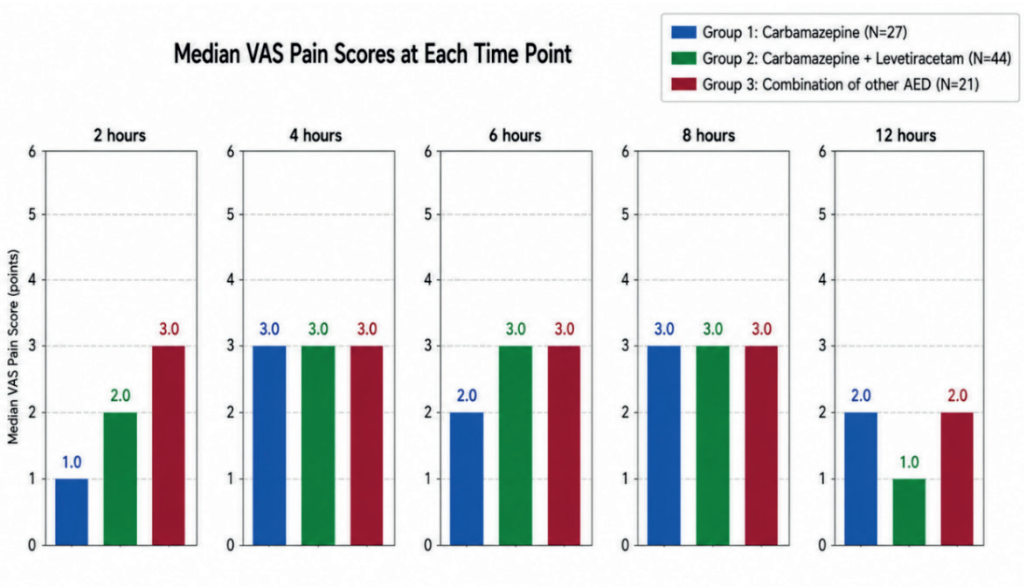

Figure 1 – Trend of median VAS over 12 hours in the postoperative period

period. When compared between the second and the third group, due to additional drug combination, patients in the third group had twice the odds of experiencing post-operative pain compared with those in the second group. However, the difference was not statistically significant (Fisher's exact test, p = 0.287). The data is illustrated in supplementary table S1.

Pain intensity measured by VAS at 2 hours postoperatively varied among the groups, being 1.0 (0.0–2.5), 2.0 (1.0–3.0), and 3.0 (2.0–4.0) in the carbamazepine, carbamazepine + levetiracetam, and other AED groups, respectively. The overall difference in pain intensity was borderline (p = 0.05). Pairwise comparison showed that the carbamazepine group had a lower pain intensity score than the other AED group (p=0.028); however, after Bonferroni adjustment, the discrepancy was not statistically significant (p=0.084).

At 4 hours, pain intensity among the groups was as follows: 3.0 (2.0–8.0), 3.0 (2.0–4.0), and 3.0 (2.0–4.0), indicating a similar distribution of pain intensity (p=0.715). At 6 hours postoperatively, median VAS scores were 2.0 (2.0–3.0), 3.0 (2.0–3.0), and 3.0 (3.0–3.0) in the carbamazepine, carbamazepine + levetiracetam, and other AED groups, respectively. Pairwise comparison showed lower pain intensity in the first group than in the third group (p = 0.05); however, after Bonferroni correction, the difference did not reach statistical significance (p = 0.075). At 8 hours postoperatively, the VAS pain score was 3.0 (2.0–3.0) in all groups (p = 0.322). While at 12 hours, the VAS pain score was comparable (p = 0.932) and tended to decline, comprising 2.0 (0.5–2.0), 1.0 (1.0–2.0), and 2.0 (1.0–2.0), respectively. Figure 1 demonstrates the VAS pain intensity trend over 12 postoperative hours.

The median number of hours to the first postoperative analgesic request was lower in the third group, 3.0 (2.0–4.75), than in the first, 4.0 (4.0–4.0), and the second, 4.0 (2.25–5.75) groups, although no statistically significant differences were noted (p = 0.35). Regarding additional analgesia, its frequency (p = 0.332) and the types of analgesia (morphine, tramadol, and NSAIDs; p = 0.68) were also comparable across the groups.

To identify predictors of postoperative pain, we performed a univariate analysis of preoperative and intraoperative factors. No significant associations were found with age, gender, BMI, epilepsy duration, main antiepileptic drug doses, anesthesia and surgery duration, anesthetic and analgesic doses, pipecuronium, ventilation time, and RASS parameter (Table S2, supplementary materials). There was no statistically significant difference in the proportion of patients with post-operative pain considering surgery types (Fisher test, p = 0.73, Table S3 supplementary material). To stabilize the statistical model, we combined rare procedures in the common category named “other procedures” which included cortical dysplasia resection (5/92), cavernous hemangioma excision (4/92), arteriovenous malformation resection (3/92), ulegyria resection (2/92). Post-operative pain occurred in 41/69 patients after lobectomy, 7/14 patients after other surgery, and 6/9 after tumor resection.

To identify more robust associations for predicting postoperative pain risk factors, multivariable logistic regression was performed on clinically relevant parameters. Considering 54 events of pain out of 92, we selected a few parameters for stable configuration of the model. Table 4 represents the results. The model included intraoperative fentanyl, antiepileptic drug regimen across three groups and type of the surgery. Carbamazepine monotherapy and lobectomy were used as references.

The model demonstrated no statistically significant independent predictors of post-operative pain. Nevertheless, compared with carbamazepine monotherapy, treatment with carbamazepine in combination with levetiracetam was associated with lower odds of post-operative pain (OR 0.46, 95% CI 0.16–1.31, p = 0.147). Patients receiving other AED medications had comparable odds of postoperative pain with carbamazepine monotherapy (OR 1.00, 95% CI 0.28–3.59, p = 0.998). Considering surgery, patients undergoing tumor resection had 42% higher odds of postoperative pain compared to the lobectomy surgery patients (OR 1.33, 95% CI 0.28–6.23,

Table 4 Multivariable regression analysis considering presence of post-op pain and intraoperative parameters

Predictor	Adjusted OR	95% CI	p-value
Fentanyl (mcg/kg)	1.04	0.96–1.13	0.316
Carbamazepine + Levetiracetam vs. Carbamazepine	0.46	0.16–1.31	0.147
Other AED vs. Carbamazepine	1.00	0.28–3.59	0.998
Other surgery vs. Lobectomy	0.74	0.21–2.58	0.631
Tumor resection vs. Lobectomy	1.33	0.28–6.23	0.717

Table 5 Multivariable regression analysis considering presence of post-op pain and other parameters

Variable	Adjusted OR	95% CI	p-value
Male vs Female	0.87	0.34–2.26	0.781
Fentanyl (per mcg/kg)	1.02	0.94–1.12	0.599
Levetiracetam vs Carbamazepine	0.47	0.19–1.18	0.109
Other surgery vs. Lobectomy	0.59	0.17–2.07	0.413
Tumor resection vs. Lobectomy	1.34	0.29–6.15	0.703

p = 0.717). On the contrary, patients undergoing cortical dysplasia resection, cavernous hemangioma excision, arteriovenous malformation resection, and ulegyria resection demonstrated 23% lower odds of post-operative pain than those undergoing lobectomy surgery (OR 0.74, 95% CI 0.21–2.58, p = 0.717).

Carbamazepine (n = 57) and levetiracetam (n = 32) were the most commonly used antiepileptic drugs as primary treatment options (89/92), whereas the sample sizes for valproic acid (n = 2) and lamotrigine (n = 1) were extremely small. We decided to investigate the incidence of postoperative pain among patients receiving two most common main antiepileptic medication. Thus, we performed the second multivariable logistic regression as a sensitivity analysis and in addition, included gender parameter to investigate the differences in pain perception, since difference in the postoperative analgesic requirements have been reported prior [21]. Table 5 demonstrates the results.

After adjustment for selected parameters, no independent predictor of postoperative pain was identified in the secondary analysis (p > 0.05 for all variables). Although non-significant, male patients showed lower odds of post-op pain than females (OR 0.87, 95% CI 0.34–2.26, p = 0.781), and patients receiving levetiracetam demonstrated lower odds of post-op pain compared to those receiving carbamazepine antiepileptic medication as a primary treatment (OR 0.47, 95% CI 0.19–1.18, p = 0.109). The odds of developing postoperative pain assuming a surgery type preserve similar trends as during primary analysis. The consistency of the findings between the primary and sensitivity analyses suggests that the exclusion of the three patients receiving other main AEDs did not significantly influence the study conclusions.

When patients were stratified by the primary antiepileptic drug. It was shown that participants receiving levetiracetam had a longer duration of epilepsy than those receiving carbamazepine: 18.0 (12.0–24.0) vs. 12.0 (6.0–18.0) years, p = 0.028. No other associations were observed.

Discussion

The retrospective cohort study evaluated how prolonged antiepileptic therapy interacts with general anesthesia agents and the potential effect of antiepileptic therapy on postoperative pain in patients with pharmacoresistant focal epilepsy. The findings show that patients receiving dual therapy have significantly longer epilepsy duration than those receiving carbamazepine monotherapy. Despite pharmacokinetic differences among the antiepileptic medications, intraoperative consumption of fentanyl, sevoflurane, propofol, and neuromuscular blocking agents is comparable across groups. Postoperative pain intensity follows a similar trajectory across groups. In multivariable analysis, duration of epilepsy and antiepileptic drug regimen do not emerge as independent predictors of postoperative pain.

In the present study, disease duration is longer in participants receiving dual therapy. This aligns with clinical reasoning: patients with longer epilepsy often require polypharmacotherapy because monotherapy becomes less effective and pharmacoresistance develops. In the study, among patients receiving antiepileptic drug treatment for more than 5 years, 59% report inefficiency of first-line antiepileptic therapy, and 70% report inefficiency of second-line antiepileptic medication. Inadequate selection of the first- and second-line treatments increases the risk of pharmacoresistance by 18- and 9-fold, respectively. Every additional year of epilepsy duration increases the risk of pharmacoresistance by 7% [22]. According to the recently conducted retrospective study, patients on polypharmacy have the onset of epilepsy at an older age and experience a higher frequency of seizures before the therapy compared to the monotherapy group. In contrast, patients on monotherapy tend to experience five years of remission and are more prone to discontinue the treatment compared to the polypharmacy group [23].

Contrary to expectations, the antiepileptic medication regimen is not significantly associated with differences in consumption of general anesthesia agents. Enzyme-inducing antiepileptic drugs, such as carbamazepine, enhance the function of cytochrome P450 enzymes [24], potentially increasing the requirements for general anesthesia agents. Exposure to long-term antiepileptic therapy may result in faster recovery after, possibly due to hepatic microsomal enzyme induction and decreased GABA receptor sensitivity [25,26]. Our findings, however, do not demonstrate a significant discrepancy in propofol or inhaled anesthetics consumption across the groups.

Previous study reports an increased intraoperative fentanyl consumption depending on the number of antiepileptic medications received by patients [27]. Conversely, in the present study, there is no statistically significant difference in fentanyl consumption between the participants receiving monotherapy or combined dual antiepileptic therapy. Extended exposure to anticonvulsant therapy may result in resistance to non-depolarizing muscle relaxants due to increased liver metabolism, acetylcholine receptors upregulation, and increased protein binding, reducing the availability of muscle relaxants [28]. In a study comparing the effect of cisatracurium among patients undergoing craniotomy, patients exposed to chronic antiepileptic medications demonstrate higher clearance and lower steady-state plasma concentration of cisatracurium than participants without a history of antiepileptic drug use [29]. In the current study, however, the statistically significant difference in pipecuronium consumption is not observed.

According to the current observations, the median post-op mechanical ventilation time in the ICU is 35% and 40% longer in the carbamazepine + levetiracetam than in the carbamazepine and other AED groups, respectively. In the second group, each patient was prescribed levetiracetam either as a primary or a secondary medication, unlike in other groups. According to a recent study, patients receiving levetiracetam have a longer interval to the next rocuronium maintenance dose than the control group, resulting in longer recovery [30]. This could be explained by potential competition for excretion via P-glycoprotein transmembrane drug efflux pump, since levetiracetam and rocuronium are transported by the same pump [30]. Delayed elimination of neuromuscular agents may result in prolonged postoperative mechanical ventilation in the ICU.

Postoperative pain is defined as acute nociceptive pain following surgical intervention because of tissue injury and

inflammatory mediator release [31]. In the present study postoperative pain is measured by VAS and ranges from 1 to 3 points, although indicating mild to moderate pain. Pain trajectories demonstrate similar trends, although patients receiving other AED medications tend to report higher pain scores at 2 and 6 hours, however, these differences lose significance after adjustment for multiple comparisons. Later during post-op period, the differences between groups decrease, also likely due to the standardized pain management protocol. In the current study the time of additional analgesic requirement is comparable across the groups, although the third group shows slightly shorter median time towards the additional analgesic requirement. This may suggest that the antiepileptic drug regimen does not significantly influence acute postoperative pain perception and is effectively managed by postoperative pain management protocols. According to a recent investigation including 42 studies, high-quality evidence demonstrates postoperative pain reduction by NSAIDs up to 24 hours in patients undergoing craniotomy [32]. In addition, pain perception may be altered in patients depending on the anatomical location of the epilepsy foci, as the recent study shows association between reduction in mechanical pain sensitivity and hippocampal damage in the patients with temporal lobe epilepsy [33]. This demonstrates that not only pharmacological interaction, but also anatomical structures involved may influence the pain perception in patients with chronic epilepsy.

A multivariable regression analysis finds no statistically significant associations between postoperative pain and intraoperative fentanyl, antiepileptic drug regimen, gender, or surgical procedure. Importantly, the similarity of the primary and secondary analyses strengthens the confidence that the observed findings are consistent after exclusion of patients receiving valproic acid or lamotrigine as a primary medication. The regression model shows a non-significant trend toward lower odds of postoperative pain among patients receiving levetiracetam as a primary antiepileptic drug in a dual combination treatment compared to carbamazepine-treated patients either as a mono or duo therapy. Investigations in the elective laparoscopic cholecystectomy report reduced postoperative pain scores as well as opioid consumption in patients receiving perioperative levetiracetam [34]. A clinical study conducted in rats demonstrates that levetiracetam possesses an antihyperalgesic effect, to a certain extent mediated by GABA, serotonin, opioid, and alpha-2-adrenergic receptors, in response to inflammatory stimuli [35]. Nevertheless, our findings did not reach statistical significance, and the observed trend should be regarded as hypothesis-generating rather than evidence of a true analgesic effect. Larger investigations are required to determine whether levetiracetam possesses clinically meaningful perioperative analgesic properties in patients with chronic epilepsy.

The type of neurosurgical procedure was not associated with the occurrence of postoperative pain in either the univariate or multivariable analyses. Although patients undergoing tumor resection demonstrated numerically higher odds of postoperative pain than those undergoing lobectomy in both analyses, the confidence interval is wide, and the association was not statistically significant. Likewise, the pooled group named other surgical procedures in both multivariable logistic regression models demonstrates lower odds of postoperative pain outcomes compared to lobectomy. It is possible that differences in surgical complexity and further tissue damage may vary among surgery types. These findings suggest that, within the scope of standardized perioperative anesthesia, surgery type may have only a limited influence on early postoperative pain. However, since the results do not reach statistical significance, larger sample size should be considered in the future. Likewise, no independent association between gender and postoperative pain is observed. While higher postoperative pain scores and greater fentanyl consumption have been reported among females undergoing laparoscopic cholecystectomy [21], the present study is not powered to detect modest gender-specific outcomes.

In the present study, epilepsy duration was not associated with postoperative pain intensity or analgesic requirements. In the study, comparing pain perception between participants with epilepsy and healthy individuals, sensitivity to pain was reduced in those with temporal lobe epilepsy and was associated with the extent of hippocampal damage [33]. The extent of hippocampal damage may indirectly reflect the frequency of epileptogenic firing and thus the duration of epilepsy. Nevertheless, evidence on the relationship between epilepsy duration and postoperative pain remains limited. Interestingly, our data shows that participants receiving levetiracetam as a first-line medication demonstrate longer duration of epilepsy compared to carbamazepine group. Overall, the second and third group representing combined therapy demonstrate longer disease course compared to carbamazepine monotherapy group, supporting the tendency of polypharmacy development with time [22]. Our findings suggest that disease chronicity alone may not be a major determinant of acute postoperative pain, instead, individual pain sensitivity [21], and perioperative analgesic strategies [32] may have greater influence on pain outcomes.

An additional notable finding was the longer hospital stay for patients on AED combinations other than carbamazepine plus levetiracetam. While the postoperative seizure rates were similar across groups, the higher seizure occurrence and more complex treatment regimens in this subgroup may contribute to the extended hospitalization. Consequently, the length of hospital stay likely reflects overall disease severity rather than solely perioperative pain or anesthetic influences. Further investigations in this direction are warranted.

The analysis indicates that none of the examined preoperative or intraoperative variables are associated with the occurrence of postoperative pain in patients with epilepsy. Recent study, however, demonstrates that preoperative high frequency heart rate variability as a mirror of the vagus nerve firing inversely and independently predicts the intensity of postoperative pain [36]. This suggests that postoperative pain following epilepsy surgery may be influenced more strongly by individual pain sensitivity, psychological characteristics, surgical site, and postoperative analgesic management. Current findings suggest that standardized anesthesia and postoperative analgesia provide effective pain control among the patients with pharmacoresistant focal epilepsy receiving continuous antiepileptic treatment. Third, anesthetic depth monitoring was not consistently available, which could impact the assessment of anesthetic requirements

Finally, due to retrospective design, the study may have been underpowered to detect moderate differences among the treatment groups. The sample size for valproic acid and lamotrigine as a primary medication was extremely small. Anesthetic depth monitoring was not consistently available, which could impact the assessment of anesthetic requirements. In addition, postoperative pain scale VAS is a subjective measure which may not always extrapolate a definitive pain status of a patient. In addition, the use of both pipecuronium and

rocuronium, according to individual anesthesiologist preference may compromise clear outcomes regarding the interaction of AED and neuromuscular blocking agents.

Conclusion

Long-term antiepileptic drug therapy, epilepsy duration, and surgical procedure were not identified as independent predictors of anesthetic consumption or early postoperative pain after epilepsy surgery. The comparable outcomes observed across treatment groups suggest that standardized perioperative anesthetic and analgesic protocols may minimize potential differences related to chronic antiepileptic therapy. Larger prospective multicenter studies are needed to confirm these observations and evaluate the influence of specific antiepileptic drugs on perioperative outcomes.

Supplementary materials

The Supplementary information includes:

• Supplementary Table S1. Post-operative pain between group II ang group III;

• Supplementary Table S2. Univariate Analysis of Factors Associated with Postoperative Pain;

• Supplementary Table S3: The presence of postoperative pain according to surgery type stratification.

This supplemental materials have been provided by the authors to give readers additional information about their work.

The file can be accessed using: https://www.editorialpark.com/download/article-supp/767/SUPPLEMENTARY-MATERIALS-JCMK-42946-2026-R3.docx.

Author Contributions: Conceptualization, M.D.; methodology, M.D. and S.S.; validation, M.D. and N.B.; formal analysis, N.B., A.Z. and M.D.; investigation, M.D. and N.B.; resources, A.A.; data curation, S.S.; writing – original draft preparation, M.D. and A.Z.; writing – review and editing, M.D., A.Z. and A.A.; visualization, N.B. and A.A; supervision, S.S.; project administration, M.D.; funding acquisition, M.D., A.A. All authors have read and agreed to the published version of the manuscript.

Disclosures: The authors have no conflicts of interest.

Acknowledgments: We sincerely thank the staff of the Epilepsy Center of Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan for their assistance in data collection and for providing access to the medical records used in this study. Their support was invaluable in enabling this research.

Funding: This research has been funded by the Ministry of Science and Higher Education of the Republic of Kazakhstan, Grant No. BR28512409.

Data availability statement: The data presented in this study are available on request from the corresponding author due to the protection of primary data.

Artificial Intelligence (AI) Disclosure Statement: The authors declare no AI Tools used for preparation of this work.

References

1. Ioannou P, Foster DL, Sander JW, Dupont S, Gil-Nagel A, Drogon O'Flaherty E, Alvarez-Baron A, Medjedovic J. The burden of epilepsy and unmet need in people with focal seizures. *Brain Behav*. 2022; 12(9): e2589. https://doi.org/10.1002/brb3.2589.
2. Jaxybayeva A, Kalinina D. Understanding the Healthcare Landscape for Pediat-ric Epilepsy Patients in Kazakhstan: Challenges and Opportunities. *Journal of Clinical Medicine of Kazakhstan*. 2025; 22(6): 103-108. https://doi.org/10.23950/jcmk/17474.
3. Villanueva V, Carreño M, Gil-Nagel A, Serrano-Castro PJ, Serratosa JM, Toledo M, Álvarez-Baróng E, Gilh A, Subías-Labazuyh S. Identifying key unmet needs and value drivers in the treatment of focal-onset seizures (FOS) in patients with drug-resistant epilepsy (DRE) in Spain through Multi-Criteria Decision Analysis (MCDA). *Epilepsy and Behavior.* 2021; 122: 108222. https://doi.org/10.1016/j.yebeh.2021.108222.
4. Mehdizadeh A, Barzegar M, Negargar S, Yahyavi A, Raeisi S. The current and emerging therapeutic approaches in drug-resistant epilepsy management. *Acta Neurol Belg*. 2019; 119: 155–162. https://doi.org/10.1007/s13760-019-01120-8.
5. Shankar R, Marston XL, Danielson V, Do Rego B, Lasagne R, Williams O, Groves L. Real-world evidence of epidemiology, patient characteristics, and mortality in people with drug-resistant epilepsy in the United Kingdom, 2011–2021. *J Neurol*. 2024; 271: 2473–2483. https://doi.org/10.1007/s00415-023-12165-4.
6. Gratrix AP, Enright SM. Epilepsy in anaesthesia and intensive care. *Continuing Education in Anaesthesia, Critical Care and Pain*. 2005; 5(4): 118–121. https://doi.org/10.1093/bjaceaccp/mki032.
7. Larkin CM, O'Brien DF, Maheshwari D. Anaesthesia for epilepsy surgery. *BJA Educ.* 2019; 19: 383–389. https://doi.org/10.1016/j.bjae.2019.08.001.
8. Dossov M, Seitenov S, Bekenova N, Kuatbay G. The Influence of Disease Du-ration in Pharmacoresistant Focal Epilepsy and Type of Antiepileptic Therapy on Intraoperative Infusion Therapy Parameters. *Journal of Clinical Medicine of Kazakhstan*. 2025; 22(6): 4–9. https://doi.org/10.23950/jcmk/17360.
9. Sainburg LE, Englot DJ, Morgan VL. The impact of resective epilepsy surgery on the brain network: evidence from post-surgical imaging. *Brain*. 2025; 148(6): 1866–1875. https://doi.org/10.1093/brain/awaf026.
10. Cohen H, Mahajna G, Ben-Shushan T, Matok I, Eyal S. The extent of cyto-chrome P450 3A induction by antiseizure medications: A systematic review and network meta-analysis. *Epilepsia*. 2024; 65(2): 445–455. https://doi.org/10.1111/epi.17822.
11. Pacchioni A, Yano JK, Assirati JA. Anesthesia for epilepsy surgery. *International Journal of Clinical Anesthesia and Research.* 2023; 7(1): 001–005. https://doi.org/10.29328/journal.ijcar.1001021.
12. Zhang Y, Li H, Zhang B, Zhang J, Li C. Efficacy and safety of levetiracetam in preventing postoperative seizures in adult patients with brain tumors: a meta-analysis. *Front Neurol.* 2025; 16: 1543905. https://doi.org/10.3389/fneur.2025.1543905.

13. In J, Huynh K, Luong J, Sooknanan D, Kinjo S. The Role of Antiepileptics for Postoperative Pain Management. Perioperative Pain Management: A Clinical Guide, 2024, p. 575–598. https://doi.org/10.1007/978-3-031-67648-2_37.
14. Venkatraghavan L, Bhardwaj S, Banik S, Chowdhury T, McAndrews MP, Valiante T. Emergence Patterns from General Anesthesia after Epilepsy Sur-gery: An Observational Pilot Study. *Asian J Neurosurg.* 2023; 18(03): 516–521. https://doi.org/10.1055/s-0043-1771365.
15. Fiore G, Porto E, Pluderi M, Ampollini AM, Borsa S, Legnani FG, Giampiccolo D, Miserocchi A, Bertani GA, DiMeco F, Locatelli M. Prevention of Post-Operative Pain after Elective Brain Surgery: A Meta-Analysis of Randomized Controlled Trials. *Medicina (Lithuania).* 2023; 59: 831. https://doi.org/10.3390/medicina59050831.
16. Pour-Rashidi A, Zandpazandi S, Hsu S, Shakeri A, Safari N, Apuzzo M, Stieg PE. Comparative analysis of monotherapy versus duotherapy with antiseizure medi-cations for intraoperative and early postoperative seizure control in glioma pa-tients undergoing awake craniotomy. *J Neurooncol*. 2025; 175: 303–312. https://doi.org/10.1007/s11060-025-05133-7.
17. Negm EM, Younus MA, Morsy AA, El Gammal SMS, El-Harrisi MA, Sameaa FAA, Rashad RAM, Elserafy TS, Gouda AM. Opioid-sparing multimodal analgesia for post-craniotomy pain: a randomized, double-blind, placebo-controlled trial. *BMC Anesthesiol.* 2025; 25: 437. https://doi.org/10.1186/s12871-025-03306-5.
18. Ahmad S, Khanna R, Onyewuenyi AC, Panos N, Breslin R, Sani S. Efficacy of an opioid-sparing analgesic protocol in pain control after less invasive cranial neurosurgery. *Pain Rep*. 2021; 6(3): e948. https://doi.org/10.1097/PR9.0000000000000948.
19. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, Dale O, De Conno F, Fallon M, Hanna M, Haugen DF, Juhl G, King S, Klepstad P, Laugsand EA, Maltoni M, Mercadante S, Nabal M, Pigni A, Radbruch L, Reid C, Sjogren P, Stone PC, Tassinari D, Zeppetella G. Use of opioid analgesics in the treatment of cancer pain: Evidence-based recommendations from the EAPC. *Lancet Oncol.* 2012; 13: e58–e68. https://doi.org/10.1016/S1470-2045(12)70040-2.
20. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal P V., Keane KA, Teso-ro EP, Elswick RK. The Richmond Agitation–Sedation Scale. *Am J Respir Crit Care Med.* 2002;166(10): 1338–1344. https://doi.org/10.1164/rccm.2107138.
21. Chae KL, Park SY, Hong JI, Yim WJ, Lee SC, Chung CJ. The effect of gender and age on postoperative pain in laparoscopic cholecystectomy: a prospective observational study. *Anesth Pain Med (Seoul)*. 2019; 14(3): 364–369. https://doi.org/10.17085/apm.2019.14.3.364.
22. Bjørke AB, Nome CG, Falk RS, Gjerstad L, Taubøll E, Heuser K. Evaluation of long-term antiepileptic drug use in patients with temporal lobe epilepsy: Assessment of risk factors for drug resistance and polypharmacy. *Seizure*. 2018; 61: 63–70. https://doi.org/10.1016/j.seizure.2018.07.011.
23. Hosny H, Elfayoumy N, Adly M, Abdelghany H. Genetic generalized epilepsy: factors associated with drug resistance polytherapy. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery.* 2023; 59: 4. https://doi.org/10.1186/s41983-022-00604-4.
24. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol.* 2006; 61: 246–255. https://doi.org/10.1111/j.1365-2125.2005.02529.x.
25. Maranhão MVM, Gomes EA, Carvalho EP. Epilepsy and Anesthesia. *Rev Bras Anestesiol.* 2011; 61(2): 232–254. https://doi.org/10.1590/S0034-70942011000200013.
26. Perks A, Cheema S, Mohanraj R. Anaesthesia and epilepsy. *Br J Anaesth.* 2012; 108: 562–571. https://doi.org/10.1093/bja/aes027.
27. Tempelhoff R, Modica PA, Spitznagel EL. Anticonvulsant therapy increases fentanyl requirements during anaesthesia for craniotomy. *Canadian Journal of Anaesthesia.* 1990; 37: 327–332. https://doi.org/10.1007/BF03005584.
28. Soriano SG, Martyn JAJ. Antiepileptic-Induced Resistance to Neuromuscular Blockers: Mechanisms and Clinical Significance. *Clin Pharmacokinet.* 2004; 43: 71–81. https://doi.org/10.2165/00003088-200443020-00001.
29. Richard A, Girard F, Girard DC, Boudreault D, Chouinard P, Moumdjian R, Bouthilier A, Ruel M, Couture J, Varin F. Cisatracurium-induced neuromuscular blockade is affected by chronic phenytoin or carbamazepine treatment in neurosurgical patients. *Anesth Analg*. 2005; 100(2): 538–544. https://doi.org/10.1213/01.ANE.0000143333.84988.50.
30. Jeon Y-J, Kim M. Effect of levetiracetam on rocuronium duration in patients undergoing cerebrovascular surgery. *Anesth Pain Med (Seoul)*. 2018; 13(4): 409–414. https://doi.org/10.17085/apm.2018.13.4.409.
31. Young A, Buvanendran A. Pain, Acute and Postoperative. Encyclopedia of the Neurological Sciences. 2014, p. 707–713. https://doi.org/10.1016/B978-0-12-385157-4.00233-5.
32. Galvin IM, Levy R, Day AG, Gilron I. Pharmacological interventions for the prevention of acute postoperative pain in adults following brain surgery. *Cochrane Database of Systematic Reviews.* 2019; 11: CD011931. https://doi.org/10.1002/14651858.CD011931.pub2.
33. Ayoub LJ, Honigman L, Barnett AJ, McAndrews MP, Moayedi M. Mechanical pain sensitivity is associated with hippocampal structural integrity. *Pain*. 2024; 165(9): 2079–2086. https://doi.org/10.1097/j.pain.0000000000003221.
34. Singh D, Kumar S, LNU B, Priye S, Prakash J. Preemptive Levetiracetam De-creases Postoperative Pain: A Double-Blind, Randomised, Control Trial. *Cureus*. 2023; 15(1): e33281. https://doi.org/10.7759/cureus.33281.
35. Micov A, Tomić M, Popović B, Stepanović-Petrović R. The antihyperalgesic effect of levetiracetam in an inflammatory model of pain in rats: Mechanism of action. *Br J Pharmacol*. 2010; 161: 384–392. https://doi.org/10.1111/j.1476-5381.2010.00877.x.
36. Caton L, Bolzon M, Boschiero D, Thayer JF, Gidron Y. Pre-surgical heart-rate variability strongly predicts less post-operative pain in patients with epilepsy. *J Psychosom Res.* 2021; 145: 110421. https://doi.org/10.1016/j.jpsychores.2021.110421.