# Duration Matters: Anticonvulsant Therapy Linked to Bone Loss in Interim Cross-Sectional Study

Длительность терапии антиконвульсантами как фактор риска потери костной ткани: промежуточные результаты наблюдательного кросс-секционного исследования

doi: 10.17816/CP15553 Original research

> Natalia Sivakova, Irina Abramova, Irina Trukhina, Varvara Rybasova, Mikhail Sorokin, Evgeny Kasyanov, Larisa Lukina, Vladimir Mikhailov, Galina Mazo V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology, Saint Petersburg, Russia

Наталия Сивакова, Ирина Абрамова, Ирина Трухина, Варвара Рыбасова, Михаил Сорокин, Евгений Касьянов, Лариса Лукина, Владимир Михайлов, Галина Мазо ФГБУ «Национальный медицинский исследовательский центр психиатрии и неврологии им. В.М. Бехтерева» Минздрава России, Санкт-Петербург, Россия

# ABSTRACT

**BACKGROUND:** Anticonvulsants are widely used in treating patients with mental and neurological disorders. Their long-term use increases the risk of a decrease in bone mineral density (BMD) and low-energy fractures. Despite the growing number of studies of drug-induced osteoporosis, the effect of anticonvulsants on bone microarchitecture remains poorly studied.

**AIM:** To study the effect of treatment duration with different generations of anticonvulsants on bone mineral density and fracture risk.

**METHODS:** We examined 100 adult patients with epilepsy who had been on anticonvulsants for more than 12 months and 58 healthy subjects who had never taken anticonvulsants. All the participants underwent a general clinical and neuropsychological assessment, as well as bone densitometry using quantitative computed tomography in three regions of interest (lumbar vertebrae L1, L2 and femoral neck).

**RESULTS:** BMD reductions were observed in 47 patients (47%) taking anticonvulsants and 29 (50%) subjects in the control group. The mean duration of anticonvulsant therapy was 8.7 years (SD=8.05) in patients with normal BMD, 10.7 years (SD=7.07) in patients with osteopenia, and 9.5 years (SD=5.24) in patients with osteoporosis. Age was found to significantly affect BMD, while the duration of anticonvulsant therapy affected it to a lesser extent. Patients taking first-generation anticonvulsants had lower BMD (p=0.018). ROC analysis confirmed the existence of a relationship between the duration of anticonvulsant therapy and the risk of fractures (p<0.001). The "duration of anticonvulsant therapy" threshold at the cut-off point corresponding to the highest Youden index value was 10 years.

**CONCLUSION:** Long-term treatment with conventional anticonvulsants adversely affects BMD and can lead to pathological bone resorption, increasing the risk of fractures in patients. New-generation anticonvulsants did not show any significant negative impact on BMD. The results of this study indicate the need for further research to better understand the effects of anticonvulsants on bone tissue.

# аннотация

**ВВЕДЕНИЕ:** Антиконвульсанты широко применяются для лечения пациентов с неврологическими заболеваниями и психическими расстройствами. Их длительный приём повышает риск снижения минеральной плотности костной ткани (МПКТ) и низкоэнергетических переломов. Несмотря на рост исследований лекарственно-индуцированного остеопороза, влияние антиконвульсантов на микроархитектонику костной ткани изучено недостаточно.

**ЦЕЛЬ:** Изучить влияние длительности приема антиконвульсантов различных поколений на МПКТ и риск развития переломов.

**МЕТОДЫ:** Обследовали 100 взрослых пациентов с эпилепсией, принимающих антиконвульсанты более 12 месяцев, и 58 здоровых участников, которые никогда не принимали антиконвульсанты. Все участники прошли общеклиническое, психиатрическое и неврологическое обследование, а также денситометрическое исследование с помощью количественной компьютерной томографии в трех точках (поясничные позвонки L1, L2 и шейка бедра).

**РЕЗУЛЬТАТЫ:** У 47 (47%) пациентов, принимающих антиконвульсанты, выявили снижение МПКТ, в контрольной группе — у 29 (50%). Средняя длительность приёма антиконвульсантов у пациентов с нормальной МПКТ составила 8,7 года (SD=8,05), с остеопенией — 10,7 года (SD=7,07), с остеопорозом — 9,5 года (SD=5,24). Установлено, что возраст значительно влияет на показатели МПКТ, а длительность приёма антиконвульсантов — в меньшей степени. Пациенты, принимающие антиконвульсанты первого поколения, имели более низкие показатели МПКТ (*p*=0,018). ROC-анализ подтвердил связь между длительность приёма антиконвульсантов и риском переломов (*p*<0,001). Пороговое значение показателя «длительность приема антиконвульсантов» в точке cut-off, которой соответствовало наивысшее значение индекса Юдена, — 10 лет.

**ЗАКЛЮЧЕНИЕ:** Длительная терапия традиционными антиконвульсантами негативно влияет на МПКТ и может приводить к патологической остеорезорбции, увеличивая риск переломов у пациентов. Антиконвульсанты нового поколения не показали выраженного негативного воздействия на МПКТ. Результаты исследования указывают на необходимость дальнейших исследований для более точного понимания влияния антиконвульсантов на костную ткань.

**Кеуwords:** epilepsy; bone mineral density; osteoporosis; osteopenia; densitometry; anticonvulsants **Ключевые слова:** эпилепсия; минеральная плотность костной ткани; остеопороз; остеопения; денситометрия; антиконвульсанты

# INTRODUCTION

Anticonvulsants are commonly used in clinical practice to treat various mental and neurological disorders. However, the use of anticonvulsants in neurology and anticonvulsants with mood-stabilizing properties in psychiatry is significantly complicated by the adverse effects of drugs that affect the quality of life and the effectiveness of therapy in patients suffering from epilepsy and mental disorders. One of the negative consequences of long-term anticonvulsant therapy in neurological and psychiatric clinics is the metabolic effect it has on the bone system, leading to the development of osteopenia and osteoporosis, which can eventually result in low-energy fractures. Studies have demonstrated a decrease in bone mineral density (BMD) and an increased risk of fractures in patients with mental disorders receiving long-term treatment with psychotropic drugs, including anticonvulsants [1, 2].

The prevailing context for the use of anticonvulsant drugs is epilepsy, a neuropsychiatric disorder affecting more than 50 million people worldwide [3]. Patients with epilepsy are a heterogeneous group characterized by variable durations and severities of the disease, as well as, in most cases, the presence of concomitant mental disorders. Today, epilepsy and its consequences represent a serious medical problem with an added socio-economic component. Most patients with epilepsy need lifelong anticonvulsant therapy for the symptomatic treatment of epileptic seizures and psychopathological disorders [4, 5].

The main goal of pharmacotherapy in epilepsy is to achieve complete remission of seizures with the lowest risk of adverse effects associated with drug therapy. Currently, about 30 anticonvulsants are in daily use worldwide. Factors usually taken into account for the choice of antiepileptic therapy include the type of seizures, the form of epilepsy, the age and sex of the patient, as well as concomitant diseases and the characteristics of the anticonvulsants, including efficacy, safety, tolerability, the pharmacological profile and availability of the drug for the patient. It is important to remember that monotherapy with an anticonvulsant cannot provide control of the patient's condition in most cases, not only in neurological practice, but also when it is used as a mood stabilizer in psychiatry. As a result, psychiatric and neurological patients usually receive multiple-drug therapy. Unlike patients with mental disorders, for whom anticonvulsants are usually combined with psychotropic drugs of other classes, the drug combination for epileptic patients can often include several anticonvulsants of different generations. This increases the cumulative adverse effects of medicinal products and, at the same time, complicates the management of adverse events through the discontinuation of antiepileptic therapy.

One of the insufficiently studied adverse effects of anticonvulsants is their negative impact on mineral and bone metabolism. On the one hand, many researchers have reported the negative effect of inducers of microsomal liver enzymes (cytochrome P450) on BMD [6]. Antiepileptic drugs increase the activity of the enzyme 25-hydroxyvitamin D<sub>3</sub> 24-hydroxylase (CYP24), which catalyzes the conversion of 25(OH)D to its inactive metabolite, 24,25-dihydrooxycholecalciferol (24,25-(OH),D,). Deficiency of the active metabolite of vitamin D, 1,25(OH)<sub>2</sub>D<sub>2</sub>, leads to decreased calcium absorption, which, in turn, increases the proliferation of parathyroid cells and parathyroid hormone secretion [6]. Such secondary hyperparathyroidism stimulates bone resorption, impairing bone remodeling and mineralization, reducing bone density, altering the bone microarchitecture, and increasing the risk of lowenergy fractures [6, 7]. On the other hand, there is evidence that long-term use of anticonvulsants (inducing and noninducing enzymes) can cause secondary osteoporosis [8]. Findings from a recent study identified drug type, dosage, treatment duration, and polytherapy as predictors of osteoporosis induced by anticonvulsant medications. The use of carbamazepine and valproic acid has been shown to be an independent factor in the development of osteoporosis, but nevertheless, these drugs are still the most widely used agents in psychiatric and neurological clinical practice [9]. Anticonvulsants with minimal enzyme-inducing activity, such as lamotrigine, are considered to be safer than conventional anticonvulsants [10]. However, despite the increasing application of new-generation anticonvulsants, data on their effect on BMD are lacking and the mechanisms of their effect on bone metabolism remain unknown [11]. Calcitonin deficiency, hyperhomocysteinemia (associated with changes in the bone microarchitecture and increased bone fragility), vitamin K and carnitine deficiency, decreased sex hormone levels, and direct effects on osteoclasts are among the hypotheses that exist to explain bone loss during anticonvulsant therapy. Anticonvulsants also have a direct effect on chondrocyte growth, especially in children, and on vitamin D and calcium levels [7]. In this regard, control of vitamin D levels in patients with mental and neurological disorders on long-term anticonvulsant therapy seems to be a rational osteoporosis prevention measure.

However, there are quite contradictory data in this area. A study conducted in India showed a significant decrease in BMD of the femoral neck in patients taking anticonvulsants, in contrast to the control group [12]. By contrast, a more recent study, also in India, did not find significant differences in BMD of the lumbar spine or femoral neck between compared groups. Computed tomography (CT) densitometry in patients with epilepsy demonstrated a negative correlation between cumulative exposure and the T-score. In patients on long-term treatment with anticonvulsants, bone tissue microarchitecture significantly changes, as evidenced by biochemical parameters and a decrease in BMD [13]. Since patients need to take anticonvulsants for a long time, often combining drugs of different generations and receiving multiple drugs simultaneously for maximum control of their condition, some researchers believe that the use of anticonvulsant therapy for  $\geq 2$  years (carbamazepine, phenobarbital, phenytoin, valproic acid) is a risk factor of increased incidence of vertebral fractures [14].

Bone loss associated with anticonvulsant therapy is usually asymptomatic and inconspicuous. Osteoporosis is usually detected only after a fracture. Vertebral compression fractures are the most common type of osteoporotic fractures and are associated with an increased risk of hip and wrist fractures. Vertebral compression fractures are often diagnosed untimely in the general population [15]. At that stage, the impairment of bone microarchitecture is already so pronounced that bone damage can occur with minimal injury or even without it. Such fractures are called pathological or low-energy fractures.

Patients with epilepsy have a six-fold increased risk of falling compared with the general population, which can increase the likelihood of injury. In addition, the incidence of osteoporosis in this group of patients is 1.7-fold higher [6]. Patients with primary mental disorders are also at an increased risk of falling compared with the general population. Their risk factors include an acute psychotic episode, bipolar affective disorder and the risky behavior associated with it, and the adverse effects of psychotropic therapy (sedation, orthostatic hypotension) [16]. Decreased BMD generally complicates the treatment of injuries in patients. Any planned surgery, whether it is the replacement of a deformed joint or osteosynthesis of a broken vertebra with metal implants, is associated with an increased risk due to bone fragility and the risk of implant migration. The combination of these factors adversely affects the quality of life of patients with mental and neurological disorders; for example, by decreasing motor activity through prolonged hospitalization and immobilization, which, in turn, exacerbates vitamin D deficiency and worsens the condition of the bone tissue [17]. It should be noted that the risk group for the development of low-energy fractures includes, in addition to elderly and very old patients, young and middle age individuals; that is, active working people, which worsens the burden of the disease.

Despite the available data describing the relationship between changes in bone and mineral metabolism in patients on long-term anticonvulsant therapy, there has been a limited number of studies in Russia that considered this aspect. The poorly understood mechanisms of the effects of anticonvulsants on bone metabolism emphasize the need for studies that evaluate the risk factors of anticonvulsantinduced osteoporosis in the Russian population.

Based on the abovesaid, the basic hypothesis of our study was as follows: long-term use of anticonvulsants adversely affects mineral metabolism, which leads to a decrease in BMD. A number of additional hypotheses were formulated: 1) last-generation anticonvulsants affect bone tissue in the same way as older products of this class, leading to pathological bone resorption; 2) long-term use of anticonvulsants increases the likelihood of fractures in patients with epilepsy, as they experience the highest exposure to regular anticonvulsant therapy.

The study aims to study the effect of treatment duration with different generations of anticonvulsants on bone

mineral density and fracture risk. To achieve this aim, the following objectives were defined:

- To study BMD using CT densitometry in epilepsy patients meeting neuropsychiatric criteria with >12 months of anticonvulsant therapy, and in relatively healthy volunteers who had not received anticonvulsant therapy.
- 2. To determine the frequency and severity of BMD loss in two compared groups (AC and NAC).
- To compare the differential impact of traditional (AC1: carbamazepine, valproic acid, benzobarbital, phenobarbital) and last-generation agents (AC2: levetiracetam, lacosamide, lamotrigine, oxcarbazepine) on BMD.
- 4. To analyze the effect of anticonvulsant therapy duration on the bone tissue condition, and to identify the relationship between the duration of anticonvulsant therapy and a decrease in BMD with the construction of a prognostic risk model for BMD changes during long-term antiepileptic therapy.
- To assess the effect of the duration of anticonvulsant therapy on the probability of fracture with the construction of a prognostic risk model for BMD changes during long-term antiepileptic therapy.

## **METHODS**

## **Study design**

An observational cross-sectional study was conducted in the two compared groups: patients with epilepsy who had received anticonvulsants for more than 12 months and healthy volunteers who had never undergone antiepileptic drugs.

### Setting

The study was conducted at the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology. Inclusion criteria for the group of patients with epilepsy:

- 1. Male and female participants aged between 21 and 60 years inclusive.
- 2. In- and outpatients.
- 3. A confirmed diagnosis of "epilepsy" (G40 according to ICD-10).
- 4. Disease duration of no less than 12 months.
- Anticonvulsant therapy duration of no less than 12 months (AC1: carbamazepine, valproic acid, benzobarbital, phenobarbital; AC2: levetiracetam, lacosamide, lamotrigine, oxcarbazepine).

- 6. Ability to read, understand, and sign the informed consent form for inclusion in the study.
- 7. Ability and willingness to comply with all study procedures in accordance with the protocol.
- Signed voluntary informed consent of the patient to participation in the study, collection of demographic and medical data, imaging studies, collection and examination of biomaterial (venous blood), as well as the processing of anonymized personal demographic and medical data.
- 9. For women of childbearing age: a negative pregnancy test.

Inclusion criteria for the group of healthy volunteers:

- Male and female participants aged between 21 and 60 years inclusive.
- 2. No current or previous anticonvulsant therapy.
- 3. Ability to read, understand, and sign the informed consent form for inclusion in the study.
- 4. Ability and willingness to comply with all study procedures in accordance with the protocol.
- Signed voluntary informed consent of the patient to participation in the study, collection of demographic and medical data, imaging studies, collection and examination of biomaterial (venous blood), as well as the processing of anonymized personal, demographic, and medical data.
- 6. For women of childbearing age: a negative pregnancy test.

Non-inclusion criteria for all study participants:

- 1. Age less than 21 years or more than 60 years.
- 2. Refusal of the patient or his/her legal guardian to participate in the study.
- 3. Presence of clinically significant, uncontrolled somatic diseases, endocrine diseases, cancer, or other progressive diseases.
- 4. Present or past use of hormone replacement therapy, glucocorticoids, heparin, antidepressants, antipsychotics.
- 5. Suicidal thoughts or aggressive behavior that require immediate medical intervention, as revealed during the assessment interview.
- 6. Severe cognitive impairment, manifested by the participant's inability to read and understand the essence of the informed consent form for participation in the study.

7. For women of childbearing age: a positive pregnancy test.

Exclusion criteria for all study participants:

- 1. Refusal to undergo protocol-specified procedures, withdrawal of consent.
- 2. Pregnancy detected during the study.
- 3. Initiation of medical use of antidepressants, antipsychotics, glucocorticoids, heparin, hormone replacement therapy.
- 4. Uncontrolled somatic diseases that interfere with participation in the study.

## Assessment tools

All study participants underwent a clinical examination with an assessment of their somatic, neurological, and psychiatric status, detailed drug history, and the collection of information on their lifestyle, social activities, and factors likely to affect bone metabolism. A case report form was developed for the study, which included anonymized data on the subjects' age, diagnosis, treatment, and previous injuries.

BMD was assessed by bone densitometry using quantitative computed tomography performed with a Canon Aquilion One 640 multidetector computed tomography system, in three regions of interest (lumbar vertebrae L1, L2 and femoral neck). CT bone densitometry data were evaluated based on the T- and Z-scores, according to the World Health Organization (WHO) classification.

## **Statistical analysis**

The study data were encoded, organized into tables, and analyzed statistically using the StatTech software, version 3.1.10. Quantitative variables were tested for distribution normality using the Shapiro-Wilk test. If the data were normally distributed, they were described by the mean (M) and standard deviations (SD), as well as the limits of the 95% confidence interval (95% CI). Non-normally distributed quantitative data were represented by the median (Me) and the lower and upper quartiles (Q1–Q3). Categorical data were expressed in absolute values and percentages. Comparison of two groups in terms of a quantitative parameter with normal distribution and equal variance was performed using the Student's t-test. For data with non-standard distribution, the Mann-Whitney U-test was used. Univariate analysis of variance was used to compare three or more groups with normal distribution, and the Kruskal-Wallis test was used for data with nonstandard distribution. Comparison of two groups in terms of a binary attribute was performed by calculating the odds ratio. Percentages were compared using Pearson's chi-square test and Fisher's exact test when analyzing four-way contingency tables. The relationship between a binary dependent variable and one or more independent variables was assessed by multivariate logistic regression. The correlation was assessed using the Spearman's rank correlation coefficient. The linear regression method was used to develop a prognostic model, and the diagnostic significance of quantitative attributes was analyzed using the ROC curve method. The ROC curve was plotted by comparing the sensitivity and specificity of the test at different cut-off points. The Youden index was used to select the optimal point on the ROC curve. Significance levels (p-values) were considered as follows: p<0.05 were significant, p < 0.01 were highly significant, and  $p \ge 0.05$  were non-significant.

# **Ethical approval**

All participants were provided full information about the study, and they gave their written consent to participate in it. The study protocol, the informed consent form, and the case report form, as well as the conduct of the study, were reviewed and approved at a meeting of the Ethics Committee of the V.M. Bekhterev National Medical Research Centre

### Table 1. General characteristics of study participants

for Psychiatry and Neurology (Minutes No. 3К-И-1/23 dated January 26, 2023).

## RESULTS

The study included 100 adult patients with epilepsy aged 21-60 years (Me=29.0; interguartile range (IQR): 25.0; 43.3) who were on long-term (more than 12 months) anticonvulsant therapy (AC group), receiving outpatient or inpatient treatment at the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology. Of these, 53 (53%) were women and 47 (47%) were men. The median duration of anticonvulsant therapy was 7 (IQR: 3; 14) years, with a minimum duration of 1 year and a maximum duration of 25 years. The control group included 58 somatically healthy volunteers aged 22-60 years (Me=29; IQR: 25; 43) who were not on anticonvulsants (NAC group) or other medications that could have affected BMD. Of these, 42 (72%) were women and 16 (28%) were men. The characteristics of the AC and NAC groups are presented in Table 1.

The distribution of study participants by age and sex in the AC and NAC groups was heterogeneous (H=4.008; p=0.045 and  $\chi^2$ =4.990; p=0.026, respectively). Although the median age and interquartile range in the AC and NAC groups were within the same age category according to WHO criteria, the distribution of participants by age was significantly different: participants aged about 40 years

Parameter		Group		All participants	Values	
		AC ( <i>n</i> =100)	NAC ( <i>n</i> =58)	( <i>n</i> =158)	values	
Age, Me (IQR)		36.0 (29.0; 43.0)	36.0 (29.0; 43.0) 29.0 (25.0; 43.3) 34.5 (26.0; 43.0)		H=4.008, <i>p</i> =0.045, ε²=0.026	
T-score, L1/L2, M (S	D)	-0.864 (1.224)	-0.724 (1.500)	-0.812 (1.329)	F=0.402, <i>p</i> =0.527, d=0.102	
Z-score, L1/L2, M (SD)		-0.550 (1.183)	-0.512 (1.129)	-0.536 (1.160)	F=0.040, <i>p</i> =0.842, d=0.033	
BMDmean, L1, M (SD)		145.850 (34.189)	142.500 (39.528)	144.620 (36.152)	F=0.314, <i>p</i> =0.576, d=0.091	
BMDmean, L2, M (SD)		145.080 (34.436)	142.138 (39.185)	144.000 (36.156)	F=0.242, <i>p</i> =0.624, d=0.080	
Sex, <i>n</i> (%)	Women	53 (53.00%)	42 (72.41%)	95 (60.13%)	·· <sup>2</sup> 4000 = 0.026 V 0.170	
	Men	47 (47.00%)	16 (27.59%)	63 (39.87%)	χ <sup>2</sup> =4.990, <i>p</i> =0.026, ν=0.178	
BMD changes on CT, <i>n</i> (%)	Normal	53 (53.00%)	29 (50.00%)	82 (51.90%)		
	Osteopenia	32 (32.00%)	21 (36.21%)	53 (33.54%)	χ²=0.294, <i>p</i> =0.863, V=0.043	
	Osteoporosis	15 (15.00%)	8 (13.79%)	23 (14.56%)		

*Note:* AC — group of patients taking anticonvulsants; NAC — group of healthy volunteers not taking anticonvulsants; BMD — bone mineral density; BMDmean — mean bone mineral density; CT — computed tomography; d (Cohen's d) — effect size;  $\varepsilon^2$  — effect size for the Kruskal-Wallis test; F — Fisher's exact test; H — Kruskal-Wallis test; IQR — interquartile range; L1 — first lumbar vertebra; L2 — second lumbar vertebra; M — mean value; M — median value; n — number of subjects; SD — standard deviation; V (Cramér's V) — effect size for contingency tables;  $\chi^2$  — Pearson's chi-squared test.



### Figure 1. Age distribution in the group of patients with epilepsy taking anticonvulsants and in the group of healthy volunteers not taking anticonvulsants.

*Note:* AC — group of patients taking anticonvulsants; Me — median value; NAC — group of healthy volunteers not taking anticonvulsants; n — number of participants; p — level of statistical significance (or p<0.05 indicates the statistical significance of the effect).

Source: Sivakova et al., 2025.

#### Table 2. General characteristics of the adjusted groups

prevailed in the AC group, whereas the NAC group had 2 peaks at approximately 25 and 60 years (Figure 1).

The identified differences are important for the analysis of the results and interpretation of the study data, given that osteoporotic disorders are age- and sex-dependent. Therefore, an additional analysis was carried out in two groups selected from the total study sample, which were comparable in terms of sex ( $\chi^2$ =0.000, p=1.000) and age (H=0.006, p=0.941). The first group included subjects treated with anticonvulsants (ACa) and consisted of 46 patients with a median age of 33 years (IQR: 26.3; 47.3), while the second group included adjusted samples of healthy subjects (NACa) and consisted of 46 subjects with a median age of 31 years (IQR: 25.3; 49.3). It should be noted that comparability of study groups in terms of key demographic characteristics minimizes the impact of potential biases and increases the integrity of the study results. Thus, NACa and ACa groups were established. Further analysis of these age- and sexmatched groups will enable a more precise assessment of the impact of anticonvulsant treatment duration on osteoporotic changes (Table 2).

Parameter		Group		All participants	Values	
		ACa ( <i>n</i> =46)	NACa ( <i>n</i> =46)	( <i>n</i> =92)		
Age, Me (IQR)		33.0 (26.3; 47.3)	31.0 (25.3; 49.3)	32.0 (26.0; 49.5)	H=0.006, <i>p</i> =0.941, ε <sup>2</sup> =0.000	
T-score, L1/L2, M	(SD)	-0.797 (1.250)	-0.884 (1.496)	-0.840 (1.371)	F=0.091, <i>p</i> =0.763, d=0.063	
Z-score, L1/L2, M	(SD)	-0.617 (1.231)	-0.601 (1.193)	-0.609 (1.206)	F=0.004, <i>p</i> =0.949, d=0.013	
BMDmean, L1, M	(SD)	146.804 (39.395)	136.413 (38.211)	141.609 (38.946)	F=1.649, <i>p</i> =0.202, d=0.268	
BMDmean, L2, M (SD)		144.783 (39.360)	137.587 (39.189)	141.185 (39.225)	F=0.772, <i>p</i> =0.382, d=0.183	
T-score, FN, Me (IQR)		-0.2 (-1.4; 0.8)	0.0 (-0.9; 1.1)	0.0 (-1.0; 0.8)	H=0.679, <i>p</i> =0.410, ε <sup>2</sup> =0.007	
Z-score, FN, M (SD)		-0.171 (1.100)	0.179 (1.068)	0.004 (1.093)	F=2.394, <i>p</i> =0.125, d=0.323	
BMDmean FN, Me (IQR)		0.8 (0.7; 0.9)	0.8 (0.7; 0.9)	0.8 (0.7; 0.9)	H=0.085, <i>p</i> =0.771, ε²=0.001	
Sex, n (%)	Women	30 (65.22%)	30 (65.22%)	60 (65.22%)		
	Men	16 (34.78%)	16 (34.78%)	32 (34.78%)	$\chi^2 = 0.000, p = 1.000, V = 0.000$	
BMD changes on CT, <i>n</i> (%)	Normal	26 (56.52%)	20 (43.48%)	46 (50.00%)		
	Osteopenia	12 (26.09%)	19 (41.30%)	31 (33.70%)	χ²=2.430, <i>p</i> =0.297, V=0.163	
	Osteoporosis	8 (17.39%)	7 (15.22%)	15 (16.30%)		

*Note:* ACa — adjusted group of patients taking anticonvulsants; NACa — adjusted group of healthy volunteers not taking anticonvulsants; BMD — bone mineral density; BMDmean — mean bone mineral density; CT — computed tomography; F — Fisher's exact test; FN — femoral neck; H — Kruskal-Wallis test; IQR — interquartile range; L1 — first lumbar vertebra; L2 — second lumbar vertebra; Me — median value; SD — standard deviation; V (Cramér's V) — effect size for contingency tables; d (Cohen's d) — effect size;  $\varepsilon^2$  — effect size for the Kruskal-Wallis test; M — mean value; *n* — number of subjects; *p* — level of statistical significance (or *p*<0.05 indicates the statistical significance of the effect);  $\chi^2$  — Pearson's chisquared test.

Patients in the AC group were divided into two subgroups depending on the generation of the anticonvulsant taken: AC1 — patients taking conventional anticonvulsants (carbamazepine, valproic acid, benzobarbital, phenobarbital): AC2 — patients taking latest generation anticonvulsants (levetiracetam, lacosamide, lamotrigine, oxcarbazepine). The AC1 subgroup included 40 patients, of whom 21 (52.5%) were male and 19 (47.5%) were female. The median age was 36 (IQR: 29.8; 42.0) years. The AC2 subgroup included 59 individuals, of whom 25 (42.4%) were men and 34 (57.6%) women. The median age was 37 (IQR: 28.5; 43.5) years. The AC1 and AC2 subgroups were comparable in terms of sex (x<sup>2</sup>=0.618, p=0.432, V=0.079) and age (H=0.572, p=0.449,  $\epsilon^2$ =0.006). The differences between the subgroups are not related to demographic factors such as sex and age, which allows to focus on the assessment of the impact of the different generations of anticonvulsants on the studied parameters. The general characteristics of the studied subgroups AC1 and AC2 are presented in Table 3.

# **Changes in bone mineral density**

Changes in BMD were assessed based on the degree of its regression: normal  $\rightarrow$  decreased  $\rightarrow$  osteopenia  $\rightarrow$  osteoporosis. BMD measurements using CT densitometry showed that 47 (47%) patients from the AC group had decreased BMD, including 32 (32.0%) patients with CT signs of osteopenia and 15 (15%) patients with CT signs of osteoporosis. In the NAC group, BMD changes were detected in 29 (50.0%) subjects and were distributed as follows: CT osteopenia was observed in 21 (36.21%) subjects; CT osteoporosis, in 8 (13.79%) subjects. The comparative analysis of the frequency of detection and the degree of BMD changes on CT between the NAC and AC groups did not reveal statistically significant differences ( $\chi^2$ =0.294, p=0.863, V=0.043) (see Table 1). The analysis of the frequency and degree of BMD changes on CT in the age- and sex- adjusted samples ACa and NACa also demonstrated no significant differences between the compared groups ( $\chi^2$ =2.430, p=0.297, V=0.163) (see Table 2).

Parameter		Subgroup		All participant	Values	
		AC1 ( <i>n</i> =40)	AC2 ( <i>n</i> =59)	( <i>n</i> =99)	Values	
Age, Me (IQR)		36.0 (29.8, 42.0)	37.0 (28.5, 43.5)	36.0 (29.0, 43.0)	H=0.572, <i>p</i> =0.449, ε²=0.006	
Duration of AC ther	apy, years, M (SD)	11.850 (9.542)	7.814 (4.950)	9.444 (7.396)	F=7.577, <i>p</i> =0.007, d=0.531	
T-score, L1/L2, M (S	D)	-1.126 (1.193)	-0.662 (1.216)	-0.850 (1.222)	F=3.518, <i>p</i> =0.064, d=0.385	
Z-score, L1/L2, M (S	D)	-0.860 (1.310)	-0.317 (1.040)	-0.536 (1.181)	F=5.247, <i>p</i> =0.024, d=0.459	
BMDmean, L1, M (SD)		137.675 (32.734)	151.932 (34.256)	146.172 (34.211)	F=4.279, <i>p</i> =0.041, d=0.426	
BMDmean, L2, M (SD)		136.425 (33.012)	151.441 (34.409)	145.374 (34.486)	F=4.690, <i>p</i> =0.033, d=0.445	
T-score, FN, M (SD)		-0.478 (1.469)	-0.010 (1.424)	-0.196 (1.453)	F=2.477, <i>p</i> =0.119, d=0.324	
Z-score, FN, M (SD)		-0.083 (1.140)	0.116 (1.104)	0.037 (1.117)	F=0.743, <i>p</i> =0.391, d=0.177	
BMDmean, FN, M (SD)		0.769 (0.156)	0.825 (0.210)	0.802 (0.191)	F=2.027, <i>p</i> =0.158, d=0.303	
Sex, <i>n</i> (%)	Women	19 (47.50%)	34 (57.63%)	53 (53.54%)	2-0 (10 m-0 422 V-0 070	
	Men	21 (52.50%)	25 (42.37%)	46 (46.46%)	χ <sup>2</sup> =0.618, <i>μ</i> =0.432, ν=0.079	
BMD changes on CT, <i>n</i> (%)	Normal	19 (47.50%)	34 (57.63%)	53 (53.54%)		
	Osteopenia	15 (37.50%)	17 (28.81%)	32 (32.32%)	χ <sup>2</sup> =1.048, <i>p</i> =0.592, V=0.103	
	Osteoporosis	6 (15.00%)	8 (13.56%)	14 (14.14%)		

Table 3. General characteristics of patients taking conventional anticonvulsants and new-generation anticonvulsants

*Note:* AC — anticonvulsants; AC1 — subgroup of patients taking conventional anticonvulsants; AC2 — subgroup of patients taking new-generation anticonvulsants; BMD — bone mineral density; BMDmean — mean bone mineral density; CT — computed tomography; d (Cohen's d) — effect size;  $\varepsilon^2$  — effect size for the Kruskal-Wallis test; F — Fisher's exact test; FN — femoral neck; H — Kruskal-Wallis test; IQR — interquartile range; L1 — first lumbar vertebra; L2 — second lumbar vertebra; M — mean value; Me — median value; *n* — number of subjects; *p* — level of statistical significance (or *p*<0.05 indicates the statistical significance of the effect); SD — standard deviation; V (Cramér's V) — effect size for contingency tables;  $\chi^2$  — Pearson's chi-squared test.

In the quantitative BMD analysis conducted in the AC and NAC groups, the mean T-score of the L1/L2 vertebrae was -0.864 (SD=1.224) in the AC group and -0.724 (SD=1.500) in the NAC group (F=0.402, p=0.527, d=0.102). The mean Z-score of the L1/L2 vertebrae was -0.550 (SD=1.183) in the AC group and -0.512 (SD=1.129) in the NAC group (F=0.040, p=0.842, d=0.033). The mean BMD of the L1 vertebra was 145.850 (SD=34.189) in the AC group and 142.500 (SD=39.528) in the NAC group (F=0.314, *p*=0.576, d=0.091). The mean BMD of the L2 vertebra was 145.080 (SD=34.436) in the AC group and 142.138 (SD=39.185) in the NAC group (F=0.242, p=0.624, d=0.080). Thus, no statistically significant differences were demonstrated between the AC and NAC groups in terms of BMD values. The mean T-scores of the L1/L2 vertebrae, Z-scores of the L1/L2 vertebrae, and BMD values (for the L1 and L2 vertebrae) in the two groups were in comparable ranges, which is confirmed by the absence of significant differences in the F-test (p>0.05) and small effect size values (d<0.2) (see Table 1).

In the adjusted samples comparable in terms of age and sex (ACa and NACa), the following results were obtained in the analysis of BMD values. The mean T-score of the L1/L2 vertebrae was –0.797 (SD=1.250) in the ACa group and –0.884 (SD=1.496) in the NACa group (F=0.091, p=0.763, d=0.063). The mean Z-score of the L1/L2 vertebrae was –0.617 (SD=1.231) in the ACa group and –0.601 (SD=1.193) in the NACa group (F=0.004, p=0.949, d=0.013). The mean BMD of the L1 vertebra was 146.804 (SD=39.395) in the ACa group and 136.413 (SD=38.211) in the NACa group (F=1.649, p=0.202, d=0.268). For the L2 vertebra, the mean values were

144.783 (SD=39.360) and 137.587 (SD=39.189), respectively (F=0.772, p=0.382, d=0.183). The median T-score of the femoral neck was –0.2 (IQR: –1.4; 0.8) in the ACa group and 0.00001 (IQR: –0.9; 1.1) in the NACa group (H=0.679, p=0.410,  $\varepsilon^2$ =0.007). The mean Z-score of the femoral neck was –0.171 (SD=1.100) in the ACa group and 0.179 (SD=1.068) in the NACa group (F=2.394, p=0.125, d=0.323). The median BMD of the femoral neck was 0.8 (IQR: 0.7; 0.9) in both groups (H=0.085, p=0.771,  $\varepsilon^2$ =0.001). Thus, the analysis of BMD values in the adjusted ACa and NACa groups also did not reveal significant differences in the T-score, Z-score or mean BMD values for the lumbar spine (L1 vertebra, L2 vertebra) or the femoral neck (see Table 2).

# Effect of the generations of anticonvulsants on bone mineral density

The mean number of years of anticonvulsant therapy was 11.850 (SD=9.542) in the AC1 subgroup and 7.814 (SD=4.950) in the AC2 subgroup, which is significantly longer treatment with conventional anticonvulsants (F=7.577, p=0.007, d=0.531).

When assessing the categorical parameters of BMD changes in the AC1 subgroup, normal bone density values were revealed in 19 (47.5%) patients, decreases to the level of osteopenia in 15 (37.5%) patients, and reductions to the level of osteoporosis in 6 (15%) patients. In the AC2 subgroup, bone density values within the normal range were revealed in 34 (57.63%) subjects, decreases to the level of osteopenia in 17 (28.21%) patients, and reductions to the level of osteoporosis in 8 (13.56%) subjects. The analysis of

Subgroup	T-score, L1/L2	Z-score, L1/L2	BMDmean,	BMDmean,	T-score	FN Z-score,	BMDmean,
	(LS means	(LS means	L1 (LS means	L2 (LS means	(LS means	FN (LS means	FN (LS means
	[95% Cl])	[95% Cl])	[95% Cl])	[95% Cl])	[95% Cl])	[95% Cl])	[95% Cl])
AC2	-0.539	-0.198	152.481	151.296	-0.043	0.030	0.784
	[-1.062, -0.016]	[-0.643, 0.248]	[137.675, 167.288]	[136.345, 166.247]	[-0.555, 0.470]	[-0.381, 0.442]	[0.711, 0.858]
Control	-0.884	-0.601	136.413	137.587	-0.119	0.179	0.773
	[-1.285, -0.483]	[-0.942, -0.259]	[125.069, 147.757]	[126.133, 149.041]	[-0.512, 0.274]	[-0.137, 0.494]	[0.716, 0.829]
AC1	-1.163	-1.212	138.737	135.526	-0.837	-0.457	0.720
	[-1.787, -0.539]	[-1.743, -0.681]	[121.086, 156.387]	[117.704, 153.349]	[-1.449, -0.226]	[-0.948, 0.034]	[0.632, 0.808]
Pr>F (Model)	0.304	0.018	0.222	0.279	0.1	0.101	0.503
Significant	No	Yes	No	No	No	No	No

Table 4. Comparison of bone mineral density data in patients taking conventional anticonvulsants and patients treated with new-generation anticonvulsants, as well as in healthy subjects

*Note*: a, b — statistically homogeneous groups identified through pairwise comparisons; AC1 — subgroup of patients taking conventional anticonvulsants; AC2 — subgroup of patients taking new-generation anticonvulsants; BMDmean — mean bone mineral density; FN — femoral neck; L1 vertebra — first lumbar vertebra; L2 vertebra — second lumbar vertebra; NAC — group of healthy volunteers not taking anticonvulsants; Pr>F (Model) — significance level (*p*), indicates a statistically significant effect at *p*<0.05.



Figure 2. Changes in bone mineral density depending on the duration of the anticonvulsant therapy.

*Note:* AC — anticonvulsants.

Source: Sivakova et al., 2025.

the frequency and degree of changes in BMD with respect to the generation of anticonvulsants did not reveal statistically significant differences in the compared subgroups AC1 and AC2 ( $\chi^2$ =1.048, p=0.592, V=0.103) (see Table 3).

In the analysis of BMD values obtained by CT densitometry, statistically significant differences were found between the AC1 and AC2 subgroups in the following parameters: the Z-score of the L1/L2 vertebrae (F=5.247, p=0.024, d=0.459), the BMDmean of the L1 vertebra (F=4.279, p=0.041, d=0.426), and the BMDmean of the L2 vertebra (F=4.690, p=0.033, d=0.445), which may indicate a lower level of bone mineralization in patients taking conventional anticonvulsants. However, no statistically significant differences were found in the other CT parameters: the T-score of the L1/L2 vertebrae (F=3.518, p=0.064, d=0.385), as well as the T-score of the femoral neck (F=2.477, p=0.119, d=0.324), the Z-score of the femoral neck (F=0.743, p=0.391, d=0.177), and the BMDmean of the femoral neck (F=2.027, p=0.158, d=0.303) (see Table 3).

Comparison of CT densitometry results in the AC1 and AC2 subgroups with the group of healthy subjects (NAC) demonstrated a more pronounced decrease in BMD in the subgroup of patients receiving conventional anticonvulsants (AC1) (Table 4).

The analysis of BMD data obtained by CT allowed a conclusion that the difference in the Z-score of the L1/L2 vertebrae was statistically significant (p=0.018). The rest of

the parameters, including the T-scores and BMDmean, did not show statistically significant differences between the groups (*p*>0.05). The results indicate a significant decrease in BMD in the subgroup of patients taking conventional anticonvulsants (AC1), as compared with AC2 and NAC. The obtained data may indicate a potentially more negative effect of conventional anticonvulsants on bone density. At the same time, no negative effect of the new-generation anticonvulsants on BMD was observed; on the contrary, they demonstrated higher mineralization compared with the control group.

# Effect of the duration of anticonvulsant therapy on bone mineral density

The analysis of BMD changes depending on the duration of anticonvulsant therapy revealed the following: the average duration of anticonvulsant therapy was 8.7 years in patients with normal bone density, 10.7 years in patients with BMD values decreased to the level of osteopenia, and 8.5 years in patients with BMD values decreased to the level of osteoporosis. No statistically significant differences in the duration of anticonvulsant therapy were found between patients with different levels of bone density ( $p_{normal}-p_{osteopenia}=0.091$ ;  $p_{normal}-p_{osteoporosis}=0.323$ ;  $p_{osteopenia}-p_{osteoporosis}=0.775$ ) (Figure 2).

An analysis of multiple linear regression was performed in order to assess the relationship between the duration of the anticonvulsant therapy and BMD, using the "sex" and "age" of participants as covariates (Table 5). For the T-score of the L1/L2 vertebrae, duration of anticonvulsant therapy had no statistically significant effect (p=0.171), while age had a significant impact (p=0.001). This suggests that age is the main factor affecting the T-score of the L1/ L2 vertebrae, and that the duration of the anticonvulsant therapy does not play a significant role; the model explains 14% of the variation (R<sup>2</sup>=0.14). A statistically significant negative relationship with the duration of the anticonvulsant therapy was shown for the Z-score of the L1/L2 vertebrae (p=0.005), while age had no significant impact (p=0.682). The obtained data may indicate that the duration of the anticonvulsant therapy decreases the Z-score of the L1/L2 vertebrae, while the model explains 8.7% of the variation (R<sup>2</sup>=0.087). For the mean BMD of the L1 vertebra, the duration of the anticonvulsant therapy showed a tendency towards significance (p=0.053); at the same time, age had a significant impact (p<0.001). This demonstrates that age is a key factor and the duration of the anticonvulsant Table 5. Regression analysis of the relationship between the duration of anticonvulsant therapy and bone mineral density assessed using computed tomography densitometry, with "sex" and "age" covariates

Parameter	R²	Duration of therapy (p-value)	Age (p-value)	Gender (p-value)	Conclusion
Z-score, L1/L2	0.14	0.171 (non-significant)	0.001 (significant)	0.270 (non-significant)	Duration has no effect, age has an effect
Z-score, L1/L2	0.087	0.005 (significant)	0.682 (non-significant)	0.583 (non-significant)	Duration <b>has a significant effect</b> (negative relationship)
BMDmean, L1	0.286	0.053 (on the edge of significance)	<0.001 (significant)	0.129 (non-significant)	Duration is weakly correlated, age is a key factor
BMDmean, L2	0.224	0.132 (non-significant)	<0.001 (significant)	0.278 (non-significant)	Duration has no effect, age has an effect
T-score, FN	0.083	0.146 (non-significant)	0.026 (significant)	0.406 (non-significant)	Duration has no effect, age has an effect
Z-score, FN	0.028	0.119 (non-significant)	0.921 (non-significant)	0.752 (non-significant)	No relationship with duration and age
BMDmean, FN	0.088	0.083 (non-significant)	0.035 (significant)	0.872 (non-significant)	No relationship with duration, age is significant

*Note:* BMDmean — mean bone mineral density; FN — femoral neck; L1 — first lumbar vertebra; L2 — second lumbar vertebra; *p*-value — significance level, indicates a statistically significant effect at p<0.05;  $R^2$  — determination coefficient.

therapy is weakly associated; the model explains 28.6% of the variation (R<sup>2</sup>=0.286). The mean BMD of the L2 vertebra was associated with the duration of therapy without a statistical significance (p=0.132), and the age was significant, again (p<0.001), and remains an important factor; the explanatory power of the model stood at 22.4% (R<sup>2</sup>=0.224). For the T-score of the femoral neck, the model explains 8.3% of the variation (R<sup>2</sup>=0.083), while duration has no effect (p=0.146), and the age remains significant (p=0.026). When analyzing the Z-score of the femoral neck, the model showed very low explanatory power (R<sup>2</sup>=0.028) and none of the factors showed a significant impact. Duration of anticonvulsant therapy was not significant for the mean BMD of the femoral neck (p=0.083), while age showed a significant impact (p=0.035). This indicates a weak relationship with the duration of anticonvulsant use, while age continues to be a significant factor; the model explains 8.8% of the variation (R<sup>2</sup>=0.088).

# Effect of the duration of anticonvulsant therapy on the risk of fracture

An analysis of the relationship between the duration of anticonvulsant therapy and the history of fractures in the AC group was performed, with 2 subgroups of patients used. Subgroup 1 included 36 people with a history of fractures, subgroup 2 consisted of 64 people without a history of fractures. In the subgroup of patients with a history of fractures, the duration of anticonvulsant therapy was 14 (8–15) years, which is statistically longer (U=50.5, p<0.001) compared with patients without fractures, 5 (3–8) years (Figure 3).

In the control group (NAC), 16 (27.6%) individuals had a history of fractures, while 42 (72.4%) subjects had had no fractures. All healthy subjects had a history of a traumatic injury leading to a fracture. Nevertheless, the NAC and AC groups had no statistically significant differences in the fracture rate ( $\chi^2$ =0.205, p=0.651).





*Note:* AC — anticonvulsants. *Source:* Sivakova et al., 2025.



Figure 4. ROC curve relating the probability of fracture and the duration of anticonvulsant therapy.

Source: Sivakova et al., 2025.

A multivariate logistic regression performed to assess the impact of the duration of AC therapy on the development of fractures, with adjustments for sex and age, revealed that the R-squared was 0.103; therefore, the resulting model can explain only 10% of the identified cases of previous fractures. The obtained model also demonstrated the absence of a statistically significant relationship between the sex, age of the participants and the history of fractures (B=-0.86, p=0.381 and B=0.16, p=0.871, respectively), but it confirmed a statistically significant relationship between the duration of anticonvulsant therapy and the development of fractures (B=0.295, p=0.03).

To more accurately determine the relationship between the probability of fractures and the duration of anticonvulsant therapy, a ROC analysis was performed (Figure 4).

The area under the ROC curve was  $0.769\pm0.052$  with a 95% CI of 0.667-0.870 (Figure 4). The obtained model demonstrates a statistically significant relationship between the probability of fracture and the duration of anticonvulsant therapy (p<0.001).

The analysis of the specificity and sensitivity of the model demonstrated that the "duration of anticonvulsant therapy" threshold at the cut-off point corresponding to the highest Youden index value was 10 years (Figure 5, Table 6). This allows one to predict the probability of fracture in patients with epilepsy who have received anticonvulsant therapy for 10 years or longer. The sensitivity and specificity of the final model were used to select the cut-off line: the highest values for both characteristics were 72.2 and 78.1%, respectively (Table 6).



Figure 5. Analysis of the sensitivity and specificity of the ROC model depending on the threshold values of the duration of anticonvulsant therapy in the group of patients with epilepsy.

*Note*: AC — anticonvulsants.

Source: Sivakova et al., 2025.

Table 6. Threshold values of the duration of anticonvulsant therapy and the probability of fracture according to the ROC model, taking into account the sensitivity and specificity

Threshold	Sensitivity (%)	Specificity (%)	PPV	NPV
14	52.8	87.5	70.4	76.7
13	55.6	82.8	64.5	76.8
12	58.3	82.8	65.6	77.9
11	63.9	81.2	65.7	80.0
10	72.2	78.1	65.0	83.3
9	72.2	75.0	61.9	82.8
8	75.0	71.9	60.0	83.6
7	77.8	64.1	54.9	83.7
6	86.1	60.9	55.4	88.6

*Note:* NPV — negative predictive value; PPV — positive predictive value. The highest values for both characteristics (sensitivity and specificity) at the same time are shown in bold.

The results of the ROC analysis indicate a significant impact of the duration of anticonvulsant therapy on the risk of fracture in the patients. It was established that with increasing duration of anticonvulsant therapy, the probability of fractures significantly increases. The obtained results emphasize the importance of considering the duration of antiepileptic therapy, along with its efficacy, when assessing potential risks and adverse effects.

# DISCUSSION

Osteoporosis represents a major public health challenge with far-reaching implications for both population health and economic systems [8, 18]. Despite expectations, the results of this study did not reveal statistically significant differences (x<sup>2</sup>=0.294, p=0.863, V=0.043) in the BMD decrease between patients receiving long-term anticonvulsant therapy and healthy subjects not taking anticonvulsants. The analysis of BMD values obtained using CT revealed that the mean T-scores and Z-scores of the L1/L2 vertebrae, as well as the mean BMD values (for the L1 and L2 vertebrae) in the two groups were in comparable ranges, which is confirmed by the absence of significant differences in the F-test (p>0.05) and small effect size values (d<0.2). Thus, the study results demonstrate that there were no significant differences in BMD changes between the AC and NAC groups. This contradicts the results of many epidemiological studies suggesting a negative effect of anticonvulsants on BMD [19]. Taking into account that the AC and NAC groups were heterogeneous in terms of sex and sex composition, we formed adjusted groups matched for sex and age. It is important to emphasize that comparability of study groups in terms of key demographic characteristics minimizes the impact of potential biases and increases the reliability of the study results. Thus, an additional analysis was performed in adjusted samples of healthy subjects (NACa) and subjects taking anticonvulsants (ACa) for a more accurate assessment of the effect of the duration of anticonvulsant therapy on changes in BMD. However, the analysis of BMD values in the adjusted ACa and NACa groups also did not reveal significant differences in the T-score, Z-score, or mean BMD values for the lumbar spine (L1 vertebra, L2 vertebra) or the femoral neck (p>0.05, d<0.2). The obtained results demonstrate that the duration of anticonvulsant therapy does not have a significant effect on BMD, which contributes to the ongoing discussion about the safety profile of these drugs in relation to bone health. Further studies with large samples and diverse demographics are needed to better understand the relationship between anticonvulsant therapy and BMD, especially taking into account individual risk factors and the pathogenic mechanisms of action of the drugs. It should be noted that these results are interim and the enrollment of study subjects is ongoing. Upon completion of data collection, we plan to conduct an indepth analysis that will provide more informative data.

The analysis of changes in BMD depending on the generation of the anticonvulsant used revealed significant

differences in CT parameters: the Z-score of the L1/L2 vertebrae (F=5.247, p=0.024, d=0.459), the BMDmean of the L1 vertebra (F=4.279, p=0.041, d=0.426), and the BMDmean of the L2 vertebra (F=4.690, p=0.033, d=0.445). These data may indicate that anticonvulsants of different generations have a heterogeneous effect on bone density, which is probably due to different mechanisms of action. In particular, there is a tendency to lower bone density in patients taking conventional anticonvulsants. This may indicate a potentially more unfavorable effect on bone tissue and the development of pathological bone resorption. At the same time, no negative effect of newgeneration anticonvulsants on BMD was observed; on the contrary, they demonstrated higher mineralization compared with the control group. However, a comparative analysis of the frequency and degree of changes in BMD showed no statistically significant differences between groups of patients taking conventional anticonvulsants (AC1) or latest generation drugs (AC2) ( $\chi$ 2=1.048, p=0.592, V=0.103). These results are consistent with the results in the study by Hamed (2016), which demonstrated no significant differences in BMD changes depending on the generation of the anticonvulsant either [8]. Given the heterogeneous results obtained, it makes sense to analyze the effect of specific groups of anticonvulsants on BMD in future studies, taking into account their different pathogenic mechanisms of action. Such studies will provide a deeper understanding of the relationship between the use of various anticonvulsants and the condition of bone tissue, which may be important for optimizing therapeutic approaches and improving the quality of life of patients.

In addition to the generation and different pathogenic mechanisms of action of anticonvulsants, the duration of their use may be a significant factor affecting bone density. A study by Fahmy et al. (2018) demonstrated a significant increase in the risk of decreased BMD with increasing duration of antiepileptic therapy, regardless of the generation of the drug used [19]. Multiple regression models were constructed to assess the relationship between decreased bone density and the duration of antiepileptic therapy. The results of a multiple linear regression analysis, which evaluated the relationship between the duration of anticonvulsant therapy and BMD using the covariates "sex" and "age" showed a significant negative relationship between the duration of anticonvulsant therapy and the BMD decrease assessed by the Z-score of the L1/ L2 vertebrae (p=0.005, R<sup>2</sup>=0.087). However, age and sex

did not have any significant effect on the Z-score of the L1/L2 vertebrae (p=0.682, p=0.583, respectively), which can be explained by the age and sex dependence of this parameter. The Z-score is based on the average agespecific values and serves for comparison with standardized population values. This approach provides greater sensitivity in detecting the influence of external factors — such as duration of medication use — on bone tissue status, taking into account the individual age characteristics of each respondent. The study also demonstrated a weak relationship between the changes in the mean BMD values of the L1 vertebra and FN and the duration of anticonvulsant therapy (p=0.053 and p=0.083). However, age had a greater effect on these parameters (p<0.001 and p=0.035). The duration of anticonvulsant therapy had no significant association with changes in BMD according to the T-score of the L1/L2 vertebrae and femoral neck, with age showing a pronounced effect on these parameters. The T-score compares the bone density with the peak bone mass of young, healthy individuals, and this makes it more sensitive to age-related changes and decreases its sensitivity to changes caused by long-term anticonvulsant therapy. We believe that the more significant relationship between the duration of anticonvulsant therapy and the Z-score, as compared with the T-score, can be explained by the fact that the Z-score is a better reflection of the impact of external factors on bone tissue, including the duration of anticonvulsant therapy, and takes into account the age-related changes by default for each respondent.

The obtained interim results emphasize the need for a more in-depth study of the effect of long-term anticonvulsant therapy on changes in BMD, taking into account both age and sex, as well as therapeutic factors in patients with psychiatric and neurological diseases, in whom long-term use of anticonvulsants for different indications may be one of the factors. In addition, understanding the relationship between anticonvulsant therapy and the condition of bone tissue may contribute to the development of preventive strategies aimed at maintaining bone health in long-term users of these drugs. This, in turn, can improve the quality of patients' life, reducing the fractures risk and related complications. Thus, this study has significant potential to improve the conduct of studies aimed at evaluating the effect of anticonvulsants on BMD and the development of pathological bone resorption.

According to the recommendations of the National Osteoporosis Foundation (NOF), individuals with a history

of fractures are at an increased risk of osteoporosis [20]. However, we have not seen any studies that examined the relationship between the duration of anticonvulsant therapy and fractures. Our study provided data on the association between the duration of anticonvulsant therapy and the history of fractures in patients with epilepsy. In the subgroup of patients with a history of fractures, the duration of anticonvulsant therapy was 14 (8–15) years, which was significantly longer (p(U) < 0.001) than in the subgroup of patients with no history of fractures (64 people), 5 (3-8) years. These results indicate that the duration of anticonvulsant therapy is a potential risk factor for the development of fractures in patients with epilepsy and other neuropsychological disorders requiring the use of anticonvulsants. The absence of such assessments in prior research underscores a critical gap, necessitating further investigation into how the duration of antiepileptic therapy affects BMD and fracture risk. Studies with a subsequent development of management strategies for patients taking anticonvulsants will help lower the risks of osteoporotic fractures and improve the quality of life of patients.

# Limitations

The presented data are an interim result of the research project "The effect of anticonvulsants on the development of osteoporosis in patients with epilepsy". The age and sex distributions are significantly different in the groups, which may be important in analyzing the results and interpreting the study data. However, the final sample of the study will include participants in groups of relatively equal sex and age distributions, and each group will include equal proportions of female and male subjects in two age categories (young age of 21–40 years and middle age of 41–60 years, according to the WHO classification). Anticonvulsants represent a heterogeneous group of medications, and the findings described in this article will be further specified for individual agents as the ongoing study progresses.

# CONCLUSION

The results of the study demonstrated that patients with epilepsy have no statistically significant differences in the BMD decrease compared with healthy subjects, which is not consistent with previous research into the effect of anticonvulsants on BMD. The study also yielded conflicting data on the effect of the duration of anticonvulsant therapy on changes in BMD. However, long-term anticonvulsant therapy was found to be associated with an increased fractures risk. The results of the study highlight the importance of further studying the impact of antiepileptic therapy on bone health and the need to develop strategies to minimize the fractures risk. The development of a set of measures to prevent anticonvulsant-induced osteoporosis is an important undertaking, since the main goals of healthcare remain the prevention and prophylaxis of diseases, and the preservation of the life quality and working ability of the population.

## **Article history**

**Submitted:** 23 Jun. 2024 **Accepted:** 22 Nov. 2024 **Published Online:** 27 Jun. 2025

**Authors' contribution:** All the authors made a significant contribution to the article, checked and approved its final version prior to publication.

**Funding:** The study was funded by the Russian Science Foundation as part of the scientific project No. 23-25-00104.

**Conflict of interest:** The authors declare no conflicts of interest.

## For citation:

Sivakova NA, Abramova IV, Trukhina IYu, Rybasova VP, Sorokin MYu, Kasyanov ED, Lukina LV, Mikhailov VA, Mazo GE. Duration Matters: Anticonvulsant Therapy Linked to Bone Loss in Interim Cross-Sectional Study. *Consortium PSYCHIATRICUM*. 2025;6(2):CP15553. doi: 10.17816/CP15553

### Information about the authors

Natalia Aleksandrovna Sivakova, MD, Cand. Sci. (Med.), Lead Researcher, Department of Treatment of Patients with Exogenous Organic Disorders and Epilepsy, V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology;

ORCID: 0000-0002-9930-0892, eLibrary SPIN-code: 4309-8739 E-mail: dr.sivakovan@gmail.com

Irina Viktorovna Abramova, Laboratory Researcher, Department of Treatment of Patients with Exogenous Organic Disorders and Epilepsy, V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology; ORCID: 0009-0008-4102-0725, eLibrary SPIN-code: 2232-0655 Irina Yurievna Trukhina, Clinical resident, Department of Treatment of Patients with Exogenous Organic Disorders and Epilepsy, V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology; ORCID: 0009-0005-4721-1977

Varvara Pavlovna Rybasova, Radiologist, Radiological diagnostics department, V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology; ORCID: 0009-0001-7692-7051 Mikhail Yurievich Sorokin, MD, Cand. Sci. (Med.), Academic Secretary, Lead Researcher, The Integrative Pharmaco-psychotherapy of Patients with Mental Disorders Department, V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology; ORCID: 0000-0003-2502-6365. eLibrary SPIN-code: 7807-4497. Scopus Author ID: 57191369987, ResearcherID: AAN-5757-2020 Evgeny Dmitrievich Kasyanov, MD, Cand. Sci. (Med.), Senior Researcher, Department of social neuropsychiatry, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology, ORCID: 0000-0002-4658-2195, eLibrary SPIN-code: 4818-2523 Larisa Viktorovna Lukina, MD, Cand. Sci. (Med.), Lead Researcher, Head of the Department of Neuroimaging Research, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology, ORCID: 0000-0001-8500-7268, eLibrary SPIN-code: 4693-5577 Vladimir Alekseevich Mikhailov, MD, Dr. Sci. (Med.), Chief Scientific Researcher, Head of the Institute of Neuropsychiatry, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology, ORCID: 0000-0002-7700-2704, eLibrary SPIN-code: 5563-1009 Galina Elevna Mazo, MD, Dr. Sci. (Med.), Chief Scientific Researcher, Deputy Director for Innovative Scientific Development, Head of the Institute of Translational Psychiatry, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology; ORCID: 0000-0001-7036-5927

\*corresponding author

#### References

- Kindras MN, Ermakova AE. [Osteoporos is a multidisciplinary problem of outpatient doctors]. In: Problema realizacii mul'tidisciplinarnogo podhoda k pacientu v sovremennom zdravoohranenii: Sbornik materialov mezhdunarodnoj nauchnoprakticheskoj konferencii. Kursk: Kurskij gosudarstvennyj medicinskij universitet; 2019. p. 51–62. Russian.
- Chandrasekaran V, Pasco JA, Stuart AL, et al. Anticonvulsant use and bone health in a population-based study of men and women: cross-sectional data from the Geelong Osteoporosis Study. BMC Musculoskelet Disord. 2021;22(1):172. doi: 10.1186/s12891-021-04042-w
- Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology. 2017;88(3):296–303. doi: 10.1212/WNL.00000000003509
- 4. Thijs RD, Surges R, O'Brien TJ, et al. Epilepsy in adults. Lancet. 2019;393(10172):689–701. doi: 10.1016/S0140-6736(18)32596-0
- Manford M. Recent advances in epilepsy. J Neurol. 2017;264(8):1811–1824. doi: 10.1007/s00415-017-8394-2
- Zhidkova IA, Kaznacheeva TV, Demidova EYu, et al. [Molecular mechanisms responsible for the impact of antiepileptic therapy on bone mineral density of epileptic patients]. Nevrologija, nejropsihiatrija, psihosomatika. 2016;(1S):59–65. Russian. doi: 10.14412/2074-2711-2016-1S-59-65
- Hamed SA, Moussa EM, Youssef AH, et al. Bone status in patients with epilepsy: relationship to markers of bone remodeling. Front Neurol. 2014;5:142. doi: 10.3389/fneur.2014.00142
- Hamed SA. Markers of bone turnover in patients with epilepsy and their relationship to management of bone diseases induced by antiepileptic drugs. Expert Rev Clin Pharmacol. 2016;9(2):267–286. doi: 10.1586/17512433.2016.1123617

- Suljic EM, Mehicevic A, Mahmutbegovic N. Effect of Long-term Carbamazepine Therapy on Bone Health. Med Arch. 2018;72(4):262–266. doi: 10.5455/medarh.2018.72.262-266
- Pilotto C, Liu JF, Walker DA, et al. Seizure characteristics and the use of anti-epileptic drugs in children and young people with brain tumours and epileptic seizures: Analysis of regional paediatric cancer service population. Seizure. 2018;58:17–21. doi: 10.1016/j.seizure.2018.03.016
- Arora E, Singh H, Gupta YK. Impact of antiepileptic drugs on bone health: Need for monitoring, treatment, and prevention strategies. J Family Med Prim Care. 2016;5(2):248–253. doi: 10.4103/2249-4863.192338
- Koshy G, Varghese RT, Naik D, et al. Derangements in bone mineral parameters and bone mineral density in south Indian subjects on antiepileptic medications. Ann Indian Acad Neurol. 2014;17(3):272–276. doi: 10.4103/0972-2327.138489
- Singla S, Kaushal S, Arora S, et al. Bone Health in Patients with Epilepsy: A Community-based Pilot Nested Case-control Study. Ann Indian Acad Neurol. 2017;20(4):367–371. doi: 10.4103/aian.AIAN\_216\_17
- 14. Schousboe JT, Binkley N, Leslie WD. Liver enzyme inducing anticonvulsant drug use is associated with prevalent vertebral

fracture. Osteoporos Int. 2023;34(10):1793–1798. doi: 10.1007/s00198-023-06820-9

- Dussault PM, McCarthy D, Davis SA, et al. High prevalence of vertebral fractures in seizure patients with normal bone density receiving chronic anti-epileptic drugs. Osteoporos Int. 2021;32(10):2051–2059. doi: 10.1007/s00198-021-05926-2
- Carpels A, de Smet L, Desplenter S, et al. Falls Among Psychiatric Inpatients: A Systematic Review of Literature. Alpha Psychiatry. 2022;23(5):217–222. doi: 10.5152/alphapsychiatry.2022.21735
- Marchenkova LA, Dobritsyna MA, Badalov NG, et al. [Analysis of the effectiveness and clinical prospects of non-medicinal methods of treatment and prevention of osteoporosis]. Osteoporoz i osteopatii. 2016;19(2):88–89. Russian. doi: 10.14341/osteo2016288-89
- Siniscalchi A, Murphy S, Cione E, et al. Antiepileptic Drugs and Bone Health: Current Concepts. Psychopharmacol Bull. 2020;50(2):36–44.
- Fahmy EM, Rashed LA, Ismail RS, et al. Evaluation of bone health among epileptic patients using biochemical markers and DEXA scan: an Egyptian study. Egypt J Neurol Psychiatr Neurosurg. 2018;54(1):10. doi: 10.1186/s41983-018-0014-2
- LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022;33(10):2243. doi: 10.1007/s00198-022-06479-8