

Impact Factor: 5.723

ISSN: 2181-0982

DOI: 10.26739/2181-0982

[www.tadqiqot.uz](http://www.tadqiqot.uz)

# JNNR

JOURNAL OF NEUROLOGY AND  
NEUROSURGERY RESEARCH



VOLUME 4, ISSUE 2

2023

# ЖУРНАЛ НЕВРОЛОГИИ И НЕЙРОХИРУРГИЧЕСКИХ ИССЛЕДОВАНИЙ

ТОМ 4 НОМЕР 2

JOURNAL OF NEUROLOGY AND NEUROSURGERY RESEARCH  
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Бухарский государственный медицинский институт и tadqiqot.uz

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Рецензируемый  
научно-практический журнал  
“Журнал неврологии  
и нейрохирургических исследований”  
Публикуется 6 раз в год  
№2 (04), 2023  
ISSN 2181-0982

### Адрес редакции:

ООО Tadqiqot город Ташкент,  
улица Амира Темура пр.1, дом-2.  
web: <http://www.tadqiqot.uz/>;  
Email: [info@tadqiqot.uz](mailto:info@tadqiqot.uz)  
Тел: (+998-94) 404-0000

Макет и подготовка к печати  
проводились в редакции журнала.

### Дизайн - оформления:

Хуршид Мирзахмедов

Журнал зарегистрирован  
в Управлении печати и  
информации г. Ташкента Рег. №  
от 01.07.2020 г.

“Неврологии и нейрохирургических  
исследований” 2/2023

### Электронная версия

журнала на сайтах:

<https://tadqiqot.uz>  
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## JOURNAL OF NEUROLOGY AND NEUROSURGICAL RESEARCH

Bukhara State Medical Institute and tadqiqot.uz

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Peer-reviewed scientific and  
practical journal "Journal of Neurology  
and Neurosurgical Research"  
Published 6 times a year  
#2 (04), 2023  
ISSN 2181-0982

### Editorial address:

Tadqiqot LLC the city of Tashkent,  
Amir Temur Street pr.1, House 2.  
Web: <http://www.tadqiqot.uz/>;  
Email: [info@tadqiqot.uz](mailto:info@tadqiqot.uz)  
Phone: (+998-94) 404-0000

Layout and preparation for printing  
held in the editorial office of the  
journal.

### Design – pagemaker:

Khurshid Mirzakhmedov

Journal is registered at the Office of  
Press and Information Tashkent city,  
Reg. No. July 1, 2020

"Neurology and neurosurgical  
research" 2/2023

### Electronic version of the

#### Journal on sites:

[www.tadqiqot.uz](http://www.tadqiqot.uz),  
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УДК: 616.853-021.64: 009.24

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## REVIEW OF THE LITERATURE ON THE POTENTIAL EFFECT OF ANTIPILEPTIC DRUGS ON THE BONE SYSTEM

<http://dx.doi.org/10.5281/zenodo.7826111>

## ANNOTATION

This publication discusses the adverse effects of antiepileptic drugs on bone tissue, which increase the risk of fractures in patients with epilepsy compared with the general population. Many studies have shown a decrease in bone mineral density, an increase in the risk of osteopenia and osteoporosis in patients receiving traditional and new AEDs. Polytherapy and duration of AED use are associated with the most significant risk of decreased bone mineral density. Nevertheless, the molecular mechanisms of the effect of various AEDs on bone tissue remain poorly understood.

**Keywords.** Epilepsy, antiepileptic drug, vitamin D deficiency, bone mineral density.

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## ОБЗОР ЛИТЕРАТУРЫ О ПОТЕНЦИАЛЬНОМ ВЛИЯНИИ ПРОТИВОЭПИЛЕПТИЧЕСКИХ ПРЕПАРАТОВ НА КОСТНУЮ СИСТЕМУ

## АННОТАЦИЯ

В данной публикации рассматриваются вопросы неблагоприятного влияния противоэпилептических препаратов на костную ткань, которые повышают риск развития переломов у пациентов с эпилепсией по сравнению с общей популяцией. Во многих исследованиях показано снижение минеральной плотности костной ткани, увеличение риска развития остеопении и остеопороза у пациентов, получающих традиционные и новые ПЭП. Политерапия и длительность приема ПЭП связаны с наиболее значительным риском снижения минеральной плотности костной ткани. Тем не менее молекулярные механизмы воздействия различных ПЭП на костную ткань остаются малоизученными.

**Ключевые слова.** Эпилепсия, противоэпилептический препарат, дефицит витамина D, минеральная плотность костей.

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## АНТИЭПИЛЕПТИК ДОРИ ВОСИТАЛАРИНИНГ СУЯК ТИЗИМИГА ТАЪСИРИ БЎЙИЧА АДАБИЁТЛАР ШАРХИ

## АННОТАЦИЯ

Ушбу мақолада антиэпилептик дориларнинг суяк тўқималарига салбий таъсири муҳокама қилинади, бу эса эпилепсия билан оғриган беморларда умумий аҳолига нисбатан суяк синиш хавфини оширади. Кўпгина тадқиқотлар суяк минерал зичлигининг пасайишини, анъанавий ва янги АЕДларни қабул қилган беморларда остеопения ва остеопороз хавфининг ошишини кўрсатди. Политерапия ва АЕДни қўллаш муддати суяк минерал зичлиги пасайишининг энг муҳим хавфи билан боғлиқ. Шунга қарамай, турли АЕДларнинг суяк тўқималарига таъсирининг молекуляр механизмлари ҳали ҳам яхши ўрганилмаган.

**Калит сўзлар.** Эпилепсия, антиэпилептик препарат, D витамини етишмовчилиги, суяк минерал зичлиги

Epilepsy remains a common neurological disease requiring long-term use of one or more antiepileptic drugs (AEDs) with high rates of side effects [1]. Worldwide, about 50 million people suffer from epilepsy, of which 25% to 40% are women of reproductive age, while in 13% of women the manifestation of the disease occurs during pregnancy. In this connection, the problems of reproductive health of women with epilepsy remain open and require further in-depth study and a special approach.

Side effects of AEDs have a significant impact on the quality of life of patients, can disrupt the functions of the endocrine system and

provoke the development of sexual disorders (hypo- or hypersexuality), obesity, hypothyroidism, polycystic ovaries, delayed sexual development, menstrual dysfunction and ovulation disorders. One area of significant interest is the effect of PEP on mineral metabolism and bone density. The adverse effects of AEDs on bone health were first reported nearly four decades ago. Since then, there has been increasing evidence linking various biochemical, metabolic, and radiological abnormalities in the bones.

Bone is a dynamic tissue that is continuously renewed throughout life. Specialized cells called osteoblasts initiate bone formation,

osteocytes make up bone, and osteoclasts resorb bone. Bone density is determined by the dynamic balance between formation and resorption. The formation of bone tissue begins with the deposition of an organic matrix by osteoblasts, followed by the process of mineralization [10].

In the work of A. Verrotti et al. the features of the organic matrix, which consists mainly of type I collagen (90–95%) with the participation of various other proteins, including osteocalcin, osteonectin, osteopontin, and thrombospondin, are described in detail [10]. The mineral part of the bone tissue is hydroxyapatite, which contains calcium and phosphorus. The concentration of these ions in blood plasma and extracellular fluid determines the rate of formation and deposition of hydroxyapatite. The physiological concentration of calcium in plasma is quite stable, varies within very narrow limits and is regulated with high accuracy. Zhidkova I.A. et al. in their studies paid special attention to the mechanism of the effect of AED on bone metabolism. It was noted that with a decrease in the concentration of ionized calcium (Ca<sup>2+</sup>) in the blood by 1–2%, it causes an immediate increase in the level of parathyroid hormone (PTH) by 40–50% [16, 17]. The action of PTH is aimed at maintaining calcium in the body and increasing its concentration in blood plasma. These effects of PTH are due to the stimulation of Ca<sup>2+</sup> resorption from bones, an increase in Ca<sup>2+</sup> absorption from the glomerular filtrate, and an acceleration of the conversion of 25-hydroxycholecalciferol (25(OH)D) to 1,25-dihydroxycholecalciferol (1,25(OH)2D3) in the proximal tubules of the renal cortex when participation of the enzyme 1 $\alpha$ -hydroxylase [18]. Regulation of 1,25(OH)2D3 synthesis in the kidneys is a direct function of PTH. In the absence of PTH, 1,25(OH)2D3 is practically not formed. The physiological role of 1,25(OH)2D3 is to stimulate calcium absorption in the intestine to the level necessary for the mineralization of the organic matrix of bone tissue. The effectiveness of this mechanism is evidenced by the fact that without the participation of vitamin D, only 10–15% of dietary calcium and 60% of phosphorus are absorbed in the intestine. The interaction between 1,25(OH)2D3 and vitamin D receptors increases the efficiency of intestinal absorption of ionized calcium (Ca<sup>2+</sup>) up to 30-40%, i.e. 2-4 times, and phosphorus - up to 80%. There is a critical limit of the concentrations of calcium and phosphorus ions, below which mineralization of the organic matrix does not occur [15].

Helen A Valsamis et al. in their publications, they repeatedly noted a number of biochemical markers that reflect the overall rate of bone remodeling. They can be divided into markers of bone formation, derived from osteoblasts, and markers of bone resorption, which are degraded products of osteoclast activity [10]. Alkaline phosphatase, osteocalcin, and type I procollagen C-terminal peptide (PICP) are markers of osteoblasts [10]. Urinary markers of bone resorption include hydroxyproline, hydroxylysine, and bone-specific hydroxypyridine collagen crosslinks. Also, bone remodeling is regulated by several hormones and growth factors, including estrogens, androgens, vitamin D, PTH, tumor necrosis factor (TNF). It should be noted that bone markers are physiologically elevated during periods of bone growth and repair.

Osteoblast functions are controlled by various growth factors, including insulin-like growth factors I and II, parathyroid hormone (PTH), and vitamin D3 [1,25(OH)2D3] [10]. Increased activity of osteoblasts leads to an increase in serum concentrations of bone-specific alkaline phosphatase and osteocalcin [10]. Histologically active

osteoblasts are distinguished by a specific skeletal form of alkaline phosphatase and parathyroid hormone and vitamin D3 receptors [10].

Many studies have shown biochemical changes such as hypocalcemia, hypophosphatemia, decreased serum levels of vitamin D metabolites, and secondary hyperparathyroidism in women receiving antiepileptic drugs. An increase in PTH is likely a secondary reaction to low vitamin D levels. These changes may increase the risk of decreased bone mineral density (BMD), osteoporosis, osteomalacia, and fractures.

It is known that there is a distinction between primary and secondary osteoporosis. Primary osteoporosis occurs when BMD decreases. And secondary osteoporosis occurs against the background of a specific pathogenetic mechanism. As many foreign researchers have shown, AEDs are a recognized factor that can contribute to the development of secondary osteoporosis. The gold standard for measuring BMD is dual-energy X-ray absorptiometry (DERA) with an accuracy of up to 99% [14]. But this method is not suitable for an immediate assessment of the adequacy of treatment, because captures changes in bone density only after a year or more.

In densitometric assessment, it is recommended to examine the lumbar spine and one or two femurs. The World Health Organization uses the T-score to define osteopenia and osteoporosis as follows:

- Normal BMD: T-score greater than -1.
- Osteopenia: T-value from -1 to -2.5.
- Osteoporosis: T score less than -2.5.

Alison Pack et al (2004) conducted studies using the DERA method and found a significant decrease in BMD in the ribs, spine and femur in people taking anticonvulsants [36].

It is known that AEDs - inducers of microsomal liver enzymes (cytochrome P450): phenobarbital, phenytoin, carbamazepine, primidone - have an adverse effect on BMD, leading to the development of osteopenia or osteoporosis.

Several studies have noted the role of polytherapy in the treatment of epilepsy and have shown that polytherapy is associated with a higher risk of bone metabolism disorders than monotherapy [34,36].

L. Tjellesen and C. Christiansen [36] back in 1982. One of the first to describe a decrease in the level of vitamin D (25(OH)D), calcium and an increase in the level of alkaline phosphatase in patients taking carbamazepine (CBZ). A decrease in vitamin D levels during CBZ monotherapy was described by S. Kim et al. [35], S. Kumandas et al. [37], S. Mintzer et al. [3]. In the study by A. Verrotti et al. [38] in patients taking CBZ showed an increase in the level of alkaline phosphatase with a change in other markers of bone formation and resorption, however, the concentration of vitamin D remained within the normal range. When studying the gender aspects of the effect of enzyme-inducing AEDs on BMD, a greater decrease in the latter and an increase in the risk of fractures in menopausal women were shown [42–44].

Over the past decade, many new approved antiepileptic drugs have emerged promising a better quality of life with fewer side effects for many people with epilepsy. However, the question now arises as to whether newer antiepileptic drugs such as lamotrigine, gabapentin, vigabatrin, levetiracetam, and topiramate cause little or no adverse bone changes. A search in the literature indicates that data on the effect of new antiepileptic drugs on bone tissue are limited and give conflicting results.

Tab.1

Classification of AEDs according to their effect on the system of microsomal liver enzymes - cytochrome P450 (according to 2011 data [19])

Cytochrome P450 inducers	Cytochrome P450 inhibitors	Cytochrome P450 non-indicating AEDs
Carbamazepine	Valproic acid	Gabapentin
Oxcarbazepine		Lamotrigine
Phenobarbital		Levetiracetam
Phenytoin		Zonisamide
Topiramate		

According to Russian authors, the decrease in BMD (osteopenia and OP) is directly dependent on the duration of the disease and ongoing antiepileptic therapy. The use of inducers of the cytochrome P450 system and polytherapy increases the risk of bone loss [5] and exacerbates calcium homeostasis disorders, leading to secondary hyperparathyroidism and the development of osteopenia [9].

Thus, the problem of the effect of AEDs on BMD in patients with epilepsy requires further in-depth study in order to determine the main

risk factors for a decrease in BMD, to identify risk groups for monitoring biochemical markers of bone metabolism and timely correction of antiepileptic therapy, and to take preventive measures to minimize the negative impact of AEDs, reducing the risk of fractures in this group of patients, which will certainly improve the quality and life expectancy of patients with epilepsy.

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ТОМ 4, НОМЕР 2

JOURNAL OF NEUROLOGY AND NEUROSURGERY RESEARCH

VOLUME 4, ISSUE 2

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