Dama International Journal of Researchers (DIJR), ISSN: 2343-6743, ISI Impact Factor: 1.018
Vol 3, Issue 02, February, 2018, Pages 40 - 46, Available @ www.damaacademia.com

The Effects of Phenytoin, Carbamazepine, and Valproate on Bone

Rizal, Diah Sri E, Devi Oktafia, Didik Hasmono
Department of Clinical Pharmacy, Faculty of Pharmacy,
Airlangga University, Surabaya,East Java, Indonesia
email: rizal.alzanzhy@gmail.com

Abstract
According to WHO data in 2016, about 50 million people hsve epilepsy worldwide, which make epilepsy one of the most common neurological diseases. Antiepileptic drugs (AED) therapy are used in the long term. Its use was reported associate with the decrease bone mineral density (BMD), calcium serum, levels of 25 (OH) D_3, the increase parathyroid hormone (PTH), changes in bone turnover and the increase risk of fracture. Phenytoin, carbamazepine and valproic acid are widely used AEDs in the world. This review investigated research data related to effects of antiepileptic drugs on the bone using BioMed Central, Pubmed and Google Schoolar database. We aimed to provide a new understanding of the effects of antiepileptic drugs (phenytoin, carbamazepine, valproate) on the increase risk of fracture.

Keywords: *Epilepsy, Antiepileptic, Fracture*

I. INTRODUCTION

According to the Word Health Organization (WHO) there are about 50 million people with epilepsy in the world, which make epilepsy one of the most common neurological diseases. Mortality rates of epilepsy in the developing countries are reported to be higher than under developed countries [(1)]. Antiepileptic drugs therapy are used over the long term with the monotherapy principle are preferable to minimize side effects and drug interactions [(2)]. Polytherapy are used based on the therapeutic response and clinical conditions of each patient [(3)]. Phenytoin, carbamazepine and valproic acid are widely used antiepilepsy (AED) drugs in the world. Long-term use of AED was reported to be associated with decreased bone mineral density (BMD), changes in bone turnover and increased risk of fractures [(4)]. The risk of fracture increased 2-6 times greater than the general population and more than 15% of fractures occurred due to pathological conditions associated with bone metabolic disorders [(5)]. Incidence of fractures are 35 percent related to seizure activity. The association of doses with fracture risk has been evaluated, there is a significantly increased risk of fracture in patients with long-term cumulative use of AED[(6)]. Bone tissue constantly remodeling throughout life. The bone remodeling cycle is performed by a bone remodeling unit (BMU) consisting of a group of osteoclasts and osteoblasts. The process of bone remodeling begins with the contraction of lining cells and osteoclast precursors. Those precursors forming multinucleate active osteoclasts that mediate bone resorption. Osteoclasts stick to bone and then process them with acid secretion and proteolytic enzymes. Osteoclasts leave the resorption site and osteoblasts enter to cover the excavated area. New bone formation process begins with secrete osteoid, which finally mineralized into new bone. After the osteoid mineralization process, the osteoblasts become flat and form a newer layer of bone cells [(7)].

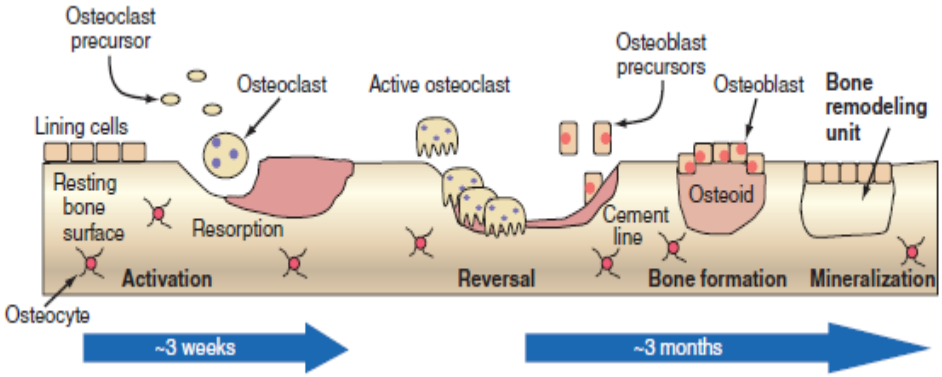

Figure 1. Schematic of Bone Remodeling Process [(7)]

This article is the result of literature study related to the effect of AED use on bone metabolism disorder studied from the results of systemic review and research studies with the aim to provide a new understanding of the effects of antiepileptic drugs on increasing the risk of fracture, especially on classic antiepileptic such as drugs phenytoin, carbamazepine and valproate. The method used in this review is systematic search of the literature on the effects of antiepileptic drugs on bone-based BioMed Central, Pubmed and Google Schoolar databases with a combination of keywords antiepileptic drugs, phenytoin, carbamazepine, valproic acid, osteoporosis, fracture, bone turnover, and

change in bone metabolism. Our literature search is limited to systemic review and research studies literature published in 2000 to 2017.

II. RESULTS AND DISCUSSION

Table 1. Effect of Antiepileptic Drugs on Bone Metabolism

Author	Clinical Parameters						Mechanism
	BMD	Calcium	25(OH)D 3	PTH	Bone Turnover	Fracture Risk (OR)	
Phenytoin							
Feldkamp *et al*, 2000 [8]		↓			bALP ↑, OC↑		- Induces CYP450 hydroxylase enzyme in the catabolism process of Vitamin D - Inhibits the absorption of calcium in the intestine and/ or decreases the active metabolite levels of Vitamin D in the tissues - Inhibits the proliferation of human osteoblasts like cells
Y. Sato *et al*, 2001 [9]	↓	↓	↓		ICTP↑		
Vestergaard *et al*, 2004[10]						1,20; 95% CI (1,00-1,43)	
Souverein *et al*, 2006 [11]						1,67; 95% CI (1,19-2,36)	
A.M. Pack *et al*, 2008 [12]	↓						
Meier & Kraenzlin, 2011[6]	↓	↓	↓	↑	bALP ↑, NTX ↑		
Carbamazepine							
Vestergaard, et al., 2004 [10]						1,18; 95% CI (1,10-1,26)	- Inducer of cytochrome P450 enzyme which leads to increased inactivation of vitamin D to calcitroic acid thus decreasing the absorption of calcium - Direct effects of carbamazepine on osteoblast proliferation
Pack, et al., 2005[13]		↓	↓	↑	bALP ↑, NTX ↑		
Borstel-Smith, et al., 2007 [14]		↓	↓				
Mintzer, et al., 2006 [15]			↓		bALP ↑, OC↑		
Souverein, et al., 2006 [11]						1.88; 95% CI (1,33–2,65)	
Lyngstad-B, et al., 2008 [16]	↓		↓		bALP↑		
Menon & Harinarayan, 2010 [17]			↓	↑			
Meier & Marius E., 2011 [6]	↓	↔	↓	↑	bALP↑, NTX ↑, ICTP↑, OC ↑		
Ahmad, et al., 2016 [18]	↓						
Valproate							
Isojärvi, et al., 2001 [19]				↔			- PTH ↑, but BMD does not decrease. This suggests that valproic acid may affect bone metabolism, but valproic acid can compensate for bone homeostasis with ↑ formation
Boluk, et al., 2004 [20]	↓			↔	ALP ↔		
Pack, et al., 2005 [13]	↔	↓	↔	↔			
Kim, et al., 2007 [21]	↔	↔	↔	↑	OC ↑		
Verrottia, et al., 2010[22]		↔	↔		bALP ↑, PICP ↑,		

					ICTP ↑, OC ↑		- Ca ↓ in patients receiving valproic acid showed that Ca levels were not only influenced by metabolism CYP450
Bauer, et al., 2013 [23]					OPG ↑, ALP ↑, RANkL ↔		
Hamed, et al., 2014 [5]	↓	↓	↓		OPG ↓, ALP ↑, sRANkL/ OPG↑, sRANkL ↑		

Abbreviations:BMD, bone mineral density; 25(OH)D3, 25-hydroxycholecalciferol, PTH, parathyroid hormone; ALP, alkaline phosphatase; bALP, bone-specific alkaline phosphatase; OC, osteocalcin; ICTP, C-terminal cross-linked type I collagen telopeptide; NTX, N-terminal cross-linked type I collagen telopeptide; PICP, Procollagen I carboxyterminal propeptide; OPG, Osteoprotegerin; sRANkL, soluble receptor activator for nuclear factor kappa β ligand; OR, Odd ratio.

A. Phenytoin

Phenytoin is an antiepileptic drug that widely prescribed to control partial-clonic and partial-complex seizure as well as the management of partial clonic seizures status epilepticus. Phenytoin is mainly have an action on the neuronal voltage-dependent sodium channels, inhibiting high voltage activated Ca^{2+} channels and potentiate GABA at $GABA_A$ receptors[24,25]. Phenytoin is metabolized in the liver primarily by CYP450 2C19, and it can also activate some transcription factor receptors such as PXR, CAR and AhR which induce the synthesis of CYP1A2, 2B6, 2C9, 3A4/5 enzymes[26,27]. The major systemic side effects of phenytoin include gingival hypertrophy, increased hair count, rash, decreased levels of folic acid and bone problems. Neurotoxic effects of phenytoin include confusion, speech impairment, double vision, ataxia and neuropathy[28]. The mechanism of the phenytoin effect on bone by inducing the CYP450 hydroxylase enzyme in the process of catabolism of vitamin D by hydroxylation of 1,25-(OH)2D into an inactive form 24,25-(OH)2D. Phenytoin directly inhibits the absorption of calcium in the gut and/ or lowers the active metabolite levels of vitamin D in the tissues through decreased levels of CaBP (calsium binding protein) and cAMP as well as Ca intake in the intestines by tissue. Phenytoin inhibits the proliferation of human osteoblast like cells thereby inhibiting the formation of new bone cells[8,29]. Several studies have shown side effect of phenytoin in bone. Case control study of 3,478 epileptic patients who experienced fractures showed an increased risk of fracture due to the use of phenytoin with OR (odd ratio) 1.67 [95% CI (confidence interval) 1.19-2.36], patients with a duration use of AED over 12 years had the greatest risk [OR 4.15 (95% CI 2.71-6.34)] and the use AED combination has a greater risk than monotherapy [OR 1.61 (95% CI 1.36-1.91)][11].

A cohort study of BMD measurements of knee and hip bones in women over 65 years suggests that there was an increased BMD loss in patients taking phenytoin compared with non-users, on knee bone [OR 1.8 (-2.68% vs -1.46%/ year $p < 0.0001$)] and hip bone [OR 1.7 (-1.16% vs -1.70% / year $p = 0.069$)] [30]. There was a decrease of BMD in patients taking phenytoine for 1 year compared with controls in healthy patients by 13% (12% in men and 15% in women, $p < 0.0001$) accompanied by decreased Z-score (-0.66 ± 1.38 vs 0.11 ± 1.28, $p < 0.001$) and T-score (-1.12 ± 1.34 vs 0.24 ± 0.48, $p < 0.001$)[9]. However, other studies suggest that a decrease BMD in young women after 1 year of phenytoin use only occurs in the femoral neck (0.023 ± 0.030 g/cm^2 or -2.6%) and not on lumbar or knee bone[12]. Several compounds have been investigated as a marker of the phenytoin side effects on bone, including osteocalcin, 25-(OH)D3, 1.25-(OH)2D, PTH, bone ALP, PICP, ICTP, calcium, magnesium and phosphate ions. Studies show decrease levels of 25-OHD and 1,25-(OH)2D in patients taking phenytoin compared with controls in healthy volunteers (12.1 ± 10.0 vs 21.6 ± 11.40 ng/ml, $p < 0.001$) [8]. Other studies have shown that patients had 25-OHD deficiency after 6 months of phenytoin therapy (29 ± 1.3 to 17.2 ± 1.6 ng / ml, $p < 0.001$)[17]. Other studies also shown that there is an increase in PTH levels in patients taking phenytoin compared with controls in healthy volunteers (31.6 ± 5.8 to 44.1 ± 14.3, $p < 0.0001$)[9]. Studies on bone ALP levels showed that there was an increase in patients taking phenytoin compared with controls in healthy volunteers (110.3 ± 50.8 to 160.7 ± 66.2 u/l, $p < 0.001$)[8]. Another marker used to measure the side effects of phenytoin in bone is ICTP, a marker of bone resorption, showing higher levels of control (4.8 ± 2.7 vs 3.5 ± 0.7, $p < 0.0001$)[9].

B. Carbamazepine

Carbamazepine is a first line therapy in the management of partial seizures as well as secondary generalized seizures. Carbamazepine primarily acts on a voltage-gated sodium channels. Carbamazepine acts on an inactivated Na^+ ion

channel, precisely at the extracellular portion of the canal, the binding of carbamazepine to the inactivated Na^+ ion channel will slow the recovery of the canal to its active form causing nerve impulses not to be delivered immediately, nerve cells not easily triggered and than prevent seizures[25,31]. Carbamazepine is an inducer of the P450 cytochrome enzyme system which have a negative impact on bone. This occurs because carbamazepine upregulates the enzyme which responsible for vitamin D metabolism, causing the conversion of 25 (OH) vitamin D into the inactive form and also causes a decrease in 1,25 $(OH)_2$ vitamin D so that the absorption of calcium in the gastrointestinal decreases, hypocalcemia, parathyroid hormone (PTH) in the circulation, increased bone resorption, and increased bone loss[6,17,18,31]. Carbamazepine belongs to a class of drugs known as xenobiotics, xenobiotics activating nuclear receptors known as steroid receptors and xecobiotic receptors (SXR) or pregnane X receptor (PXR)[13]. One study showed that xenobiotics upregulates 25(OH)D_3-24-hydroxylase (CYP24) in the kidney via PXR activation, this enzymes catalyze the conversion of 25(OH)D into the inactive metabolite (24,25-dihydroxyvitamin)[32]. Other studies have shown that xenobiotic activation may increase the expression of CYP3A4 isoenzymes in the liver and small intestine, the CYP3A4 enzymes converts vitamin D into a more polar inactive metabolite[33]. Carbamazepine also gives a direct effect on the osteoblast proliferation at a concentration equivalent to the therapeutic dose of epilepsy management[8].

The use of carbamazepine as antiepileptic drug was reported to be positively correlated with decreased BMD [6,16,18], decreased in serum calcium level[13,14], decreased 25(OH)D_3 levels [6,13–17], increased PTH (parathyroid hormone)[6,13,17], and increased bone turnover (bALP, NTX, OC, ICTP)[6,13,15,16]. Lyngstad-B, et al., (2008) reported a decrease of BMD in the use of carbamazepine monotherapy in proximal forearm from 0.60 (0.50-0.74) g/cm^2 to 0.53 (0.45-0.72) g/cm^2 ($p \leq 0.01$)[16]. Carbamazepine positively correlated with increased risk of fracture. A case-control pharmacoepidology study with outcome fracture and use of antiepileptic drugs as control (124,655 cases and 373,962 controls) showed that carbamazepine increased fracture risk by OR 1.18, 95% CI, 1.10 -1.26[10]. A cohort study over a period of 8 years with a study population consisting of 1,018 cases and 1,842 corresponding controls, the risk of fracture increases with the duration use of antiepileptic, the association was strongest in use> 12 years withOR 4.15 (95% CI 2.71-6.34) $p < 0.001$on carbamazepine there was an increased risk of fracture by OR 1.88 (95% CI 1.33-2.65) $p <0.001$[11].

C. Valproate

Valproate is an antiepileptic drug with broad spectrum used in patients with absence seizures, myoclonic seizures, tonic-clonicseizures, especially those that are primarily generalized, a few patients with atonic attacks may also respond, and some evidence suggests that the drug is effective in partial seizures. Valproate may be used as monotherapy as well as in combination with other AEDs [34]. Valproate with molecular formula $C_8H_{15}NaO_2$ has a molecular weight of 166.196 g/mol [35].Valproate is one of a series of fatty carboxylic acids that have antiseizure activity, this activity appears to be greatest for carbon chain lengths of five to eight atoms, while the double bond decreases its activity[36]. Valproate have an action on voltage-dependent sodium channels. Voltage-dependent sodium channels are in one of three basic conformation states: resting, open, and inactive. During one depolarizing cycle, voltage-dependent sodium channels pass through these three conformational states in sequence (resting-open, open-inactive, inactive-resting) and the depolarization response does not occur until it return to inactive-resting status. Valproate has a large affinity on the binding protein channels when it is inactive so the conformation process runs slowly [37].The second mechanism relates to increasing levels of GABA neurotransmitters which are the enzyme inhibitors of succinic-semialdehyde dehydrogenase. Valproate also reduces glutamate excitatory neurotransmitter levels [38].

Mechanisms involving the effects of valproic acid on bone metabolism are a direct effect on bone cells. Several invitro studies have reported the direct effects of valproate acid on bone cells, because valproic acid acts as a histone deacetylase (HDAC) inhibitor [39]. HDAC performs histone deacetylase by removing the acetyl group from the lysine residue on the histone. The HDAC process blocks gene transcription. Valproic acid can induce inhibition of HDAC, histone acetylation, accumulation of hiperasetilasi will causes interference of cellular functions such as cell differentiation and apoptosis [40]. Valproat also has another mechanism on bone that is an effect on decreasing active metabolite of vitamin D, although valproic acid are not included in a group of drug inhibitor enzyme CYP450 but several studies have shown that valproic acid can induce the catabolic enzyme of vitamin D [5,39]. Indirect effects on bone metabolism through endocrine function, a study about the long term use of valproic acid in men affected hypothalamic-pituitary-gonadal axis [41], whereas in women associated with regulation of menstrual cycle, polycystic ovarian syndrome, hyperandrogenism [39]. Valproate was reported to be positively correlated with a decrease in BMD [5,20]; decreased serum calcium [5,13]; decreased levels of 25(OH)D_3 [5]; increased levels of PTH [21]; and inreased level of bone turnover (bALP, ALP, NTX, OC, PICP, ICTP, sRANkL) [5,21–23]. Several studies have reported the effects of valproate on bone. A prospective study was conducted on 31 adult patients newly diagnosed with epilepsy receiving oxcarbazepine therapy (n = 16, mean age 45.6 years) or valproate (n = 15, mean age 42.2 years). Calcium, phosphate,

ALP, RANKL, OPG, OC and cathepsin K were analyzed at 2 weeks and 3 months of therapy. In patients with valproate therapy, the OPG increased 0.07 mmol/L (p = 0.004) after 3 months of therapy although the other markers showed no significant differences [(23)].

The study involved 25 post-pubertal males, newly diagnosed of epilepsy with an average age of 16.5 to 22.1 years and 20 control of healthy post-pubertal male, measured parameters of bone metabolism and bone turn-over. After 12 months of treatment with valproate, the patient had increased formation parameters and bone resorption compared with baseline values (bone-ALP: 51.2±9.9 vs 57.3±9.3 u/ l, p <0.01; OC: 8.1±1.1 vs 10.4±1.5 lg/l, p <0.01; PICP: 138.7±16.4 vs 152.6±17.1 lg/l, p <0.01; ICTP: 3.8±0.8 vs 5.9±0.6 lg/l, p <0.01) [(22)]. Comparative cross-sectional case-control studies were conducted in 75 adult patients aged 20-50 years and 6-25 years of age. Patients received therapy at least 6 months before being included in the study, 23 patients in valproate therapy, 40 patients with carbamazepine and 12 patients with valproate + carbamazepine, and 40 healthy patients as control. The results were compared with controls, patients with valproate therapy were significantly lower in BMD (p <0.001; p <0.0001), BMC (p <0.001; p <0.001), Z-score (p <0.0001; p <0.0001), and T-score (p <0.0001; p <0.0001). Laboratory results showed significantly lower levels of serum calcium (p <0.0001), 25(OH)D (p <0.0001), OPG (p <0.001), whereas higher levels in ALP (p <0.001), sRANKL (p <0.0001), and RANKL/OPG (p < 0.0001) [(5)].

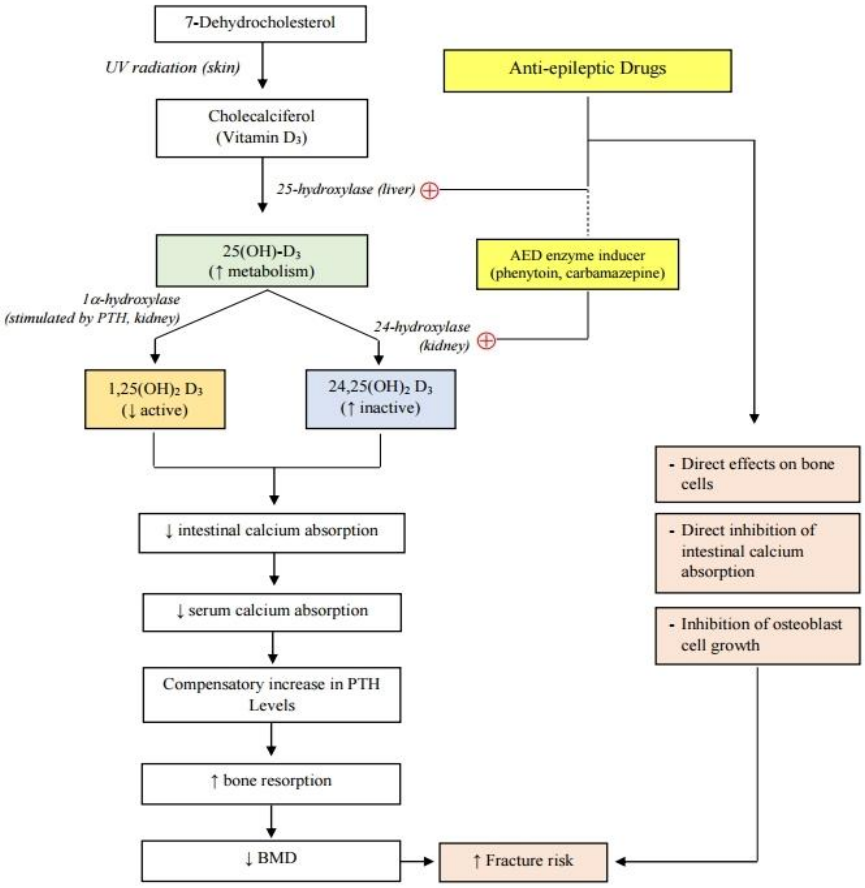

Figure 2. Mechanism of antiepileptic drug (AED) on induced fracture risk

III. CONCLUSION

Long-term use of AED, especially AED inducer of cytochrome P450 enzyme (phenytoin, carbamazepine) and valproate positively correlated with decreased bone mineral density (BMD), decreased serum calcium, decreased levels of $25(OH)D_3$, increased parathyroid hormone, changed bone turnover and increased risk of fractures.

The mechanism of actions of AED on the increased risk of fracture are the AED inducer enzyme cytochrome P450 which induces inactivation of vitamin D into calcitroic acid thus reducing absorption of calcium intestinal, AED can also cause direct inhibition on absorption of calcium intestinal, direct effects on bone and inhibition of osteoblast cell growth.

Patients with a history of prolonged use of AED (> 5 years), especially those using an AED inducer of hepatic enzymes or valproate, with risk factors (high doses of multidrug AED regimens, low vitamin D intake, limited exposure to sun, patients with chronic diseases, old of age, low physical activity, the use of drugs that induce chronic metabolic acidosis, and therapy with another drugs that induce hepatic enzymes), or with osteoporosis risk factors, suggested for BMD testing and recommended for supplementation of calcium and vitamin D.

IV. CONFLICT OF INTEREST

The author (s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. WHO. Epilepsy [Internet]. 2017 [cited 2017 Aug 23]. Available from: http://www.who.int/mediacentre/factsheets/fs999/en/
2. Lowenstein DH. Seizures and Epilepsy. In: Kasper, D; Fauci, A; Hauser, S; Longo, D.L; Jameson, L.J; Losalzo J, editor. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw-Hill Education; 2015. p. 2542–59.
3. Perdossi. Pedoman Tatalaksana Epilepsi. 5th ed. Surabaya: Airlangga University Press; 2014.
4. Zhang Y, Zheng YX, Zhu JM, Zhang JM, Zheng Z. Effects of antiepileptic drugs on bone mineral density and bone metabolism in children: A meta-analysis. J Zhejiang Univ Sci B. 2015;16(7):611–21.
5. Hamed SA, Moussa EMM, Youssef AH, Abd ElHameed MA, NasrEldin E. Bone status in patients with epilepsy: relationship to markers of bone remodeling. Front Neurol. 2014;5(August):142.
6. Meier C, Kraenzlin ME. Antiepileptics and bone health. Ther Adv Musculoskelet Dis. 2011;3(5):235–43.
7. Bringhurst, F. Richard; Demay, Marie B; Krane, S.M; Kronenberg H. Bone and Mineral Metabolism in Health and Disease. In: Kasper, Dennis L; Hauser, S.L; Jameson, J.L; Fauci, A.S; Longo, D.L; Loscalzo J, editor. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw-Hill Education; 2015. p. 2454–66.
8. Feldkamp J, Becker A, Witte OW, Scharff D, Scherbaum WA. Long-term anticonvulsant therapy leads to low bone mineral density--evidence for direct drug effects of phenytoin and carbamazepine on human osteoblast-like cells. Exp Clin Endocrinol Diabetes. 2000;108(1):37–43.
9. Sato Y, Kondo I, Ishida S, Motooka H, Takayama K, Tomita Y, et al. Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. Neurology. 2001;57(3):445–9.
10. Vestergaard, P; Rejnmark, L; Mosekilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia. 2004;45(11):1330–7.
11. Souverein PC, Webb DJ, Weil JG, Van Staa TP, Egberts ACG. Use of antiepileptic drugs and risk of fractures: Case-control study among patients with epilepsy. Neurology. 2006;66(9):1318–24.
12. Pack A, Morrell M, Randall A, McMahon D, Shane E. Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. Neurology. 2008;70(18):1586–93.
13. Pack AM, Morrell MJ, Marcus R, Holloway L, Flaster E, Done S, et al. Bone mass and turn over in woman with epilepsy on epileptic drug monotherapy. Ann Neurol. 2005;57(2):252–7.
14. von Borstel Smith M, Crofoot K, Rodriguez-Proteau R, Filtz TM. Effects of phenytoin and carbamazepine on calcium transport in Caco-2 cells. Toxicol Vitr. 2007;21(5):855–62.
15. Mintzer S, Boppana P, Toguri J, DeSantis A. Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. Epilepsia. 2006;47(3):510–5.
16. Lyngstad-Brechan MA, Taubøll E, Nakken KO, Gjerstad L, Godang K, Jemtland R, et al. Reduced bone mass and increased bone turnover in postmenopausal women with epilepsy using antiepileptic drug monotherapy. Scand J Clin Lab Invest. 2008;68(8):759–66.

17. Menon B, Harinarayan C V. The effect of anti epileptic drug therapy on serum 25-hydroxyvitamin D and parameters of calcium and bone metabolism-A longitudinal study. Seizure. British Epilepsy Association; 2010;19(3):153–8.
18. Shiek Ahmad B, O'Brien TJ, Gorelik A, Hill KD, Wark JD. Bone Mineral Changes in Epilepsy Patients During Initial Years of Antiepileptic Drug Therapy. J Clin Densitom. Elsevier Inc.; 2016;19(4):450–6.
19. Isojärvi JIT, Turkka J, Pakarinen AJ, Kotila M, Rättyä J, Myllylä V V. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. Epilepsia. 2001;42(7):930–4.
20. Boluk A, Guzelipek M, Savli H, Temel I, Ozişik HI, Kaygusuz A. The effect of valproate on bone mineral density in adult epileptic patients. Pharmacol Res. 2004;50(1):93–7.
21. Kim SH, Lee JW, Choi K-G, Chung HW, Lee HW. A 6-month longitudinal study of bone mineral density with antiepileptic drug monotherapy. Epilepsy Behav. 2007;10(2):291–5.
22. Verrotti A, Agostinelli S, Coppola G, Parisi P, Chiarelli F. A 12-month longitudinal study of calcium metabolism and bone turnover during valproate monotherapy. Eur J Neurol. 2010;17(2):232–7.
23. Bauer S, Hofbauer LC, Rauner M, Strzelczyk A, Kellinghaus C, Hallmeyer-Elgner S, et al. Early detection of bone metabolism changes under different antiepileptic drugs (ED-BoM-AED)--a prospective multicenter study. Epilepsy Res. Elsevier B.V.; 2013;106(3):417–22.
24. Kwan P, Sills GJ, Brodie MJ. The mechanisms of action of commonly used antiepileptic drugs. Pharmacol Ther. 2001;90(1):21–34.
25. Lacy CF., Amstrong LM., Goldman MP., Lance LL. Drug Information Handbook. 26th ed. USA: Lexi-Comp Inc; 2017.
26. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: Cause for concern? Epilepsia. 2013;54(1):11–27.
27. Cuttle L, Munns AJ, Hogg NA, Scott JR, Hooper WD, Dickinson RG, et al. Phenytoin Metabolism By Human Cytochrome P450: Involvement of P450 3a and 2C Forms in Secondary Metabolism and Drug-Protein Adduct Formation 1. 2000;28(8):945–50.
28. Schachter SC., Garcia P., Eichler AF. Antiseizure drugs: Mechanism of action, pharmacology, and adverse effects. UpToDate. 2017.
29. Fitzpatrick LA. Pathophysiology of bone loss in patients receiving anticonvulsant therapy. Epilepsy Behav. 2004;5 Suppl 2:S3-15.
30. Ensrud, K.E.; Walczak, T.S.; Blackwell, T.; Ensrud, E.R.; Bowman, P.J.; Stone KL. Antiepileptic drug use and rates of hip bone loss in older men: a prospective study. Neurology. 2008;71(10):723–30.
31. Verrotti A, Coppola G, Parisi P, Mohn A, Chiarelli F. Bone and calcium metabolism and antiepileptic drugs. Clin Neurol Neurosurg. 2010;112(1):1–10.
32. Pascussi JM, Robert A, Nguyen M, Walrant-Debray O, Garabedian M, Martin P, et al. Possible involvement of pregnane X receptor-enhanced CYP24 expression in drug-induced osteomalacia. J Clin Invest. 2005;115(1):177–86.
33. Zhou C, Assem M, Tay JC, Watkins PB, Blumberg B, Schuetz EG, et al. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. J Clin Invest. 2006;116(6):1703–12.
34. Aminoff MJ., Douglas VC. Nervous System Disorders. In: Papadakis, M.A.; McPhee SJ, editor. CURRENT Medical Diagnosis & Treatment. New York: McGraw-Hill Education; 2017. p. 977–1049.
35. Sweatmen CS. Martindale, The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
36. McNamara JO. Pharmacotherapy of te Epilepsies. In: Brunto, L.L.; Lazo, J.S.; Parker KL., editor. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill Medica; 2011. p. 583–608.
37. Rollins DE., Blumenthal DK. Workbook and Casebook For Goodman and Gilman's The Pharmacological Basis of Therapeutics. 1st ed. New York: McGraw-Hill Education; 2016.
38. Eadie M., Vajda F. Antiepileptic Drugs and Pregnancy - A Guide for Prescribers. Switzerland: Springer; 2016.
39. Pitetzis DA, Spilioti MG, Yovos JG, Yavropoulou MP. The effect of VPA on bone: From clinical studies to cell cultures-The molecular mechanisms revisited. Seizure. BEA Trading Ltd; 2017;48:36–43.
40. Sun L, Coy DH. Modern Chemistry & Applications Anti-Convulsant Drug Valproic Acid in Cancers and in Combination Anti- Cancer Therapeutics. 2014;2(1):1–5.
41. Verrotti A, Loiacono G, Laus M, Coppola G, Chiarelli F, Mario G. Hormonal and reproductive disturbances in epileptic male patients : Emerging issues. Reprod Toxicol. Elsevier Inc.; 2011;31(4):519–27.