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Review Article

The Association Between Antiepileptic Drugs and Bone Health

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Abstract

Bone and calcium metabolism disorders are emerging as major issues in the treatment of pediatric patients with epilepsy because children in this stage experience rapid growth, weight gain, and skeletal and genital maturation under the influence of several hormones. There is a relatively complex and multifaceted relationship among epilepsy, antiepileptic drugs (AEDs), and bone and calcium homeostasis. Whether classical AEDs (e.g., benzodiazepines, carbamazepine, phenytoin, phenobarbital, and valproic acid) or newer AEDs (e.g., levetiracetam, oxcarbazepine lamotrigine, topiramate, gabapentin, and vigabatrin) can adversely affect bone health remain unclear. Cytochrome P450 induction, which is one of the properties of AEDs, can cause vitamin D deficiency and lead to lower calcium levels, lower bone mass, increased fracture risk, and altered bone turnover. However, controversial results have been obtained because of the wide spectrum of the antiseizure activities of these AEDs with several different mechanisms of action, which are discussed in this review.

Key words: Bone, calcium metabolism, epilepsy, antiepileptic drugs, cytochrome P450

Introduction

In addition to determining the height, bones also protect the vital organs and provide support for movement. Although stiff and unyielding, bones are living tissues that are continuously remodeled throughout a person's life. Constant remodeling renews the skeleton and modulates calcium and phosphorus homeostasis. This is critical for the specialized cells engaged in bone remodeling and turnover processes, such as in osteoblasts (initiate bone formation), osteocytes (monitor bone mechanical stresses), and osteoclasts (absorb bone)[1]. These processes are intricately modulated by several hormonal factors that are highly dependent on the phase of the life cycle. The rate of annual calcium turnover is 100% in infants and 18% in adults. Up to 95% of total bone development is completed by the age of 18 years[2]. Therefore, childhood and adolescence are most critical periods during which bone is accrued. Any factor interfering with bone homeostasis may affect the bone health.

Epilepsy is one of the most frequently occurring neurological disorders, affecting approximately 50 million people worldwide. The estimated average prevalence of epilepsy in the US is 6.8 per 1000 people, compared with 5.5 per 1000 people in Europe, 1.5–14 per 1000 people in Asia, and 2.8 per 1000 people in Taiwan[3, 4]. As part of the management of patients with seizures, clinicians should perform a thorough medical evaluation including a detailed description of the seizure semiology; the assessment of present, past, and family history; physical examination; laboratory analysis; awake and sleep electroencephalograms; and brain magnetic resonance imaging. Appropriate classification of the seizure type and epileptic syndrome is essential in

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the treatment of epilepsy. Although numerous alternative treatment options are available for epilepsy, including vagus nerve stimulation, epilepsy surgery, and ketogenic diets, approximately 50% of patients with newly diagnosed epilepsy are successfully controlled with the use of adequate antiepileptic drugs (AEDs)[5]. Hence, AEDs represent the primary treatment of choice.

Skeletal disorders are reported in patients with epilepsy, and restrictions of physical activity imposed by seizures or coexisting neurologic deficits, inadequate sunlight exposure, and poor diet appear to be the causes. To date, it is difficult to conclude whether the changes in bone and calcium metabolism are attributable to epilepsy itself or the use of AEDs. Some of these changes are, at least to some extent, AED-related. AED administration has been continually linked to adverse effects on bone health and affect patients of both sexes and at all ages[6]. Classical AEDs such as benzodiazepines (BZDs), carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), and valproic acid (VPA) are reported to decrease bone mineralization, and their ability to degrade vitamin D by inducing cytochrome P450 (CYP) isoenzymes is believed to the main mechanism[7]. Newer AEDs, such as levetiracetam (LEV), oxcarbazepine (OXC), lamotrigine (LTG), topiramate (TPM), gabapentin (GBP), and vigabatrin (VGB), have been developed to improve the treatment of refractory seizures as well as the tolerability and safety. However, both classical and newer AED can cause adverse bone effects[6]. Clinicians should pay more attention to the use of AEDs in children and adolescents because of the rapid growth in this period and the particular vulnerability of these age groups to effects on the skeleton.

Numerous techniques have been used to obtain histologic and radiographic evidence of bone abnormalities in patients receiving AEDs, ranging from bone biopsies to dual-energy X-ray absorptiometry (DXA), the present gold standard for detecting decreases in *bone* mineral density (BMD). Early reports suggested that 65–84% of patients with epilepsy who are receiving AEDs develop signs of bone abnormalities, such as rickets, osteomalacia, osteoporosis, and increased fracture risk[6, 8]. Rickets is a disorder of defective mineralization of cartilage in the epiphyseal growth plates of children, leading to widening of the ends of long bones, growth delay, skeletal deformities, and delayed developmental milestones. Bone biopsy reveals the accumulation of unmineralized bone, and biochemical findings include low calcium, phosphorous, and vitamin D metabolite levels and elevated alkaline phosphatase content[9]. Osteomalacia is a metabolic disorder caused by deficiency of vitamin D or its metabolites, which leads to the failure of mature bone to mineralize and the eventual softening of bones. Drug-induced osteomalacia occurs secondary to either deficiencies in calcium, phosphate, and active vitamin D or interference with their deposition or activity. Osteomalacia is linked to signs such as diffuse bone pain, muscle weakness, and bone fragility[10]. Osteoporosis is a disease characterized by low bone mass and reduced bone quality, leading to increased bone fragility and risk of fracture, particularly of the hips, spine, and wrists. Often, there are no symptoms until the first fracture occurs[11]. Apart from eliminating other causes of medical illness, particularly malabsorption, renal disease, and hepatic disease, AED-induced skeletal diseases should be considered in patients receiving AEDs for epilepsy who experience bone pain, muscle weakness, fractures after minimal trauma, or worsening of seizure control. Failure to recognize these issues may lead to the deterioration of patients' conditions.

BMD reflects a complex, dynamic, highly orchestrated process between bone resorption by osteoclasts and the bone-formative action of osteoblasts. A higher of BMD demonstrates the bone in the healthy milieu. Routine X-rays can identify bone fractures, but they cannot not measure bone density. DXA is a low-radiation X-ray technique capable of detecting small percentages of bone loss, and it is the gold standard for measuring BMD. DXA can measure the bone density of the whole skeleton, and the most common sites for clinical use are the spine and hips. Apart from the advantage of detecting minor bone changes, DXA can identify patients at risk of future osteoporosis and provide effective information for protecting against further bone loss. Little is known about the mechanisms by which AEDs cause unfavorable bone changes. Several studies using DXA to measure BMD in patients receiving AEDs for epilepsy revealed significantly reduced BMD at the ribs, spine, femoral neck, and hips and reduced BMD at axial and appendicular sites in children[6, 7]. Markers of bone turnover including markers of bone formation and resorption, which usually increase in osteoporosis, are elevated

in persons with epilepsy who are receiving AEDs[6, 12]. Therefore, these results raise serious concerns about the bone disorders and calcium metabolism of patients with epilepsy who use AEDs and highlight the need to closely monitor growth in children and adolescents with epilepsy. Physicians should be aware of these issues.

The aim of this paper was to provide physicians a short review concerning the impact of classical and newer AEDs on skeletal diseases and calcium metabolism and emphasize the need for a much higher index of suspicion of this entity to ensure timely withdrawal of AEDs and appropriate therapy to avoid serious disabilities.

BZDs are common psychoactive drugs that are widely used to treat anxiety, insomnia, agitation, seizures, status epilepticus, acute repetitive seizures, muscle spasms, alcohol withdrawal, and premedication for some medical or dental procedures. The main effects of BZDs include the enhancement of levels of the neurotransmitter gamma-aminobutyric acid (GABA) and GABA-A receptor-mediated chloride conductance, leading to sedative, hypnotic, anxiolytic, anticonvulsant, and muscle-relaxant effects[13, 14]. The most commonly used BZDs are diazepam, lorazepam, and clonazepam. The core chemical structure of BZDs is a benzene ring fused to a diazepine ring, and their advantages in clinical use include high efficacy rates, a rapid onset of action, and minimal toxicity. Reports revealed that BZDs increase the risk of fractures, and a positive correlation between fracture risk and increasing dose, especially regarding the spine, through mechanisms including reduced BMD, reduced 25OHD, and increased alkaline phosphatase (ALP) levels has been described[12, 15-17]. Conversely, BZD-related bone disorders are not related to the levels of total calcium, phosphorus, magnesium, and parathyroid hormone (PTH); however, controversial results have been reported[8, 18].

CBZ, an iminodibenzyl derivative, is a commonly used medication for partial seizures and secondary generalized seizures in adults and children. More than 90% of countries list CBZ as an essential drug for their populations' health. CBZ is extensively metabolized in the liver, and the main metabolite is CBZ-10, 11-epoxide, which possesses anticonvulsant properties. Additionally, CBZ mainly acts on voltage-gated sodium channels that are stabilized in their inactivated state, reduces polysynaptic responses, and blocks post-tetanic potentiation. CBZ may cause several adverse effects, including sedation, ataxia, dizziness, nausea, vomiting, constipation, diarrhea, altered metabolism of lipids, changes in sex hormone levels, hyponatremia, weight gain, anemia, agranulocytosis, and allergic reactions[6, 19]. CBZ is reported to cause spina bifida in neonates exposed to the drug in utero[20]. Several studies revealed that CBZ can decrease BMD in the lumbar spine, femoral neck, and forearms. That is because CBZ can induce CYP isoenzymes, possibly reducing vitamin D levels[21, 22]. Additionally, high levels of markers of bone formation (bone ALP, osteocalcin, carboxy-terminal propeptide of type I procollagen, and amino-terminal propeptide of type III procollagen) and bone resorption (carboxy-terminal telopeptide of type I collagen and the

BZDs

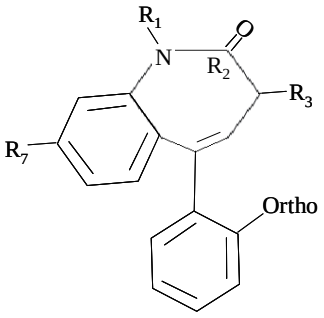

Fig. 1 Structural formula of 1,4-benzodiazepines.

CBZ

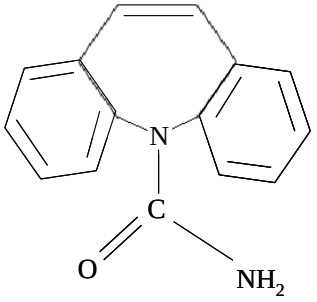

Fig. 2 Structural formula of carbamazepine.

PHT

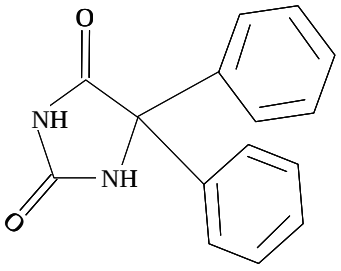

Fig. 3 Structural formula of phenytoin.

urinary cross-linked N-telopeptides of type I collagen [NTx]) were detected patients receiving CBZ, but their vitamin D levels were normal[12]. Interestingly, CBZ may have a direct effect on bone cell proliferation, leading to reduced growth of human bone cells[23].

PHT is a hydantoin that was identified to have hypnotic effects on electroshocks inducing seizures in cats. PHT is used to treat generalized tonic–clonic seizures and status epilepticus, and its primary pharmacological effects possibly include promoting Na^+, K^+, and Ca^{2+} ion conductance, reducing membrane action potential, and altering amino acid concentrations to block hyperexcitability caused by excessive stimulation or environmental changes capable of reducing the membrane electrochemical gradient rather than increasing the seizure threshold and abolishing the primary focus of discharge[24]. The bioavailability of oral PHT is high, but the time to peak blood levels ranges from 3 to 12 h. The half-life of PHT is 12–36 h. Reports found that patients who receive PHT for epilepsy may have reduced lumbar spine, femur, and hip BMD[17]. PHT induces CYPs, leading to increased catabolism of vitamin D and eventual hypocalcemia[25]. PHT interferes with intestinal calcium absorption in rats, leading to lower calcium levels in serum[26]. Animal studies also revealed a direct inhibitory effect of PHT on calcitonin secretion, which affects bone resorption and formation[23, 27-29]. Patients treated with PHT exhibited elevated levels of markers of bone turnover in the serum, including markers of bone formation and bone resorption[23, 27, 28, 30, 31]. Clinically, patients with hyperparathyroidism display biochemical abnormalities, including higher PTH, ALP, and urinary NTx levels, and histological findings such as osteomalacia, suggesting that hyperparathyroidism can primarily activate bone resorption. An in vitro study uncovered that fetal rats treated with PHT exhibited an impaired osteoblastic response to PTH[23], suggesting the drug directly modulates bone metabolism. In conclusion, although there are some contradictory results regarding the links of PHT with adverse effects on bone mineralization and an increased risk of fractures, accumulating evidence illustrated that PHT can induce several abnormalities in bone metabolism including hypocalcemia, hypophosphatemia, reduced serum levels of biologically active vitamin D metabolites, hyperparathyroidism, and elevated levels of markers of bone turnover. Therefore, monitoring the bone mineral status and prophylactic prescription with vitamin D to patients with high bone fracture risk due to anticonvulsant therapy may prevent the possible development of bone disease.

PB, a compound containing a perhydropyrimidine ring substituted at C-2, C-4, and C-6 by oxo groups, has been used since the early twentieth century because it effectively reduces anxiety, promotes sleep, induces general anesthesia, and inhibits tonic–clonic seizures[32]. PB enhances GABA-mediated increases in chloride conductance by prolonging the duration of channel opening, leading to the effective control of seizures. The World Health Organization recommends PB as a first-line treatment for convulsive seizures in resource-poor countries[33]. Studies have found that PB can increase the risks of rickets and hypocalcemia, resulting from decreases in vitamin D levels due to CYP inhibition, impaired intestinal calcium transport, and increased PTH levels. Consequently, bone mineralization was reduced, and osteomalacia developed[34, 35]. However, several studies evaluating vitamin D levels in ambulatory patients reported conflicting results[17, 35-37].

VPA (2-propylpentanoic acid) was originally synthesized as an analog of valeric acid extracted from Valeriana officinalis[38]. VPA is a broad-spectrum AED against several seizure types, including absence,

PB

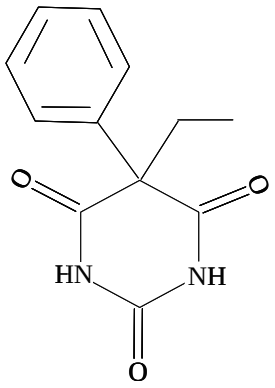

Fig. 4 Structural formula of phenobarbital.

VPA

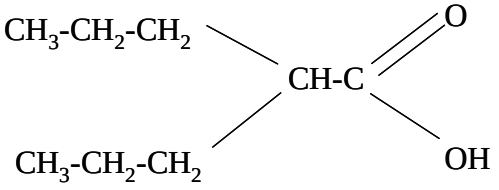

Fig. 5 Structural formula of valproic acid.

partial, and tonic–clonic seizures, and it is also effective against a variety of psychiatric and neurological diseases such as bipolar disorder, antidepressive effects, migraine, personality disorders, mental disability, dementia, and cognitive problems, in addition to use as a potential chemotherapeutic agent[38, 39]. VPA is reported to elevate GABA levels in plasma and in several brain regions by affecting the GABAergic system, inhibiting succinate semialdehyde dehydrogenase and GABA transaminase, upregulating glutamate decarboxylase, affecting cerebral metabolism by inhibiting alpha-ketoglutarate dehydrogenase in the TCA cycle, and activating GABA receptors[38-40]. VPA can block sodium channels and modulate calcium and potassium conductance and dopaminergic and serotoninergic transmission[38-40]. The effect of VPA on the regulation of glutamate excitatory neurotransmission and/or GABA inhibitory neurotransmission is one of the main mechanisms of its "mood-stabilizing" effect and its effects in the treatment of migraine. GABA-mediated responses, as well as the ability of BZD to prolong the decay time of the post-synaptic inhibitory response by interacting with the BZD regulatory site of the GABA-A receptors and increasing baclofen binding to GABA-B receptors, may be involved in the beneficial effects of VPA on neuropathic pain. VPA is an effective inhibitor of histone deacetylases, the key enzymes for controlling histone acetylation and hence the epigenetic regulation of gene expression, leading to the modulation of cell growth, differentiation, and apoptosis and thereby providing novel strategies for regulating neuroprotective genes and excitotoxicity and treating tumors[41]. Pharmacodynamically, VPA is well absorbed in all oral dosage forms, with greater than 90% bioavailability. Structurally, VPA is related to free fatty acids, and it is highly ionized at physiological pH; therefore, it exhibits a high degree of binding to plasma proteins. VPA is metabolized via microsomal glucuronidation, mitochondrial beta-oxidation, and CYP oxidation[6, 40]. The most common side effects of VPA are nausea, vomiting, abdominal cramps, diarrhea, body weight gain, impaired coagulation system, and neutropenia. Its serious adverse effects include hepatotoxicity, pancreatitis, teratogenicity, endocrine disturbances such as menstrual abnormalities, increased total testosterone levels, and obesity. VPA is reported to decrease[42], not change[43], or increase bone turnover[44-46]. Likewise, the reported effects of VPA on cultured bone cells range from inhibition of both osteoblast and osteoclast activity[47] to enhancement of osteogenesis[48]. Results by Wu et al.[49] and our group[50] suggest that VPA has direct effects on bone growth. In vivo studies investigating the effect of VPA on bone metabolism are limited. In view of the diverse molecular and cellular reactions underlying several seizure types and diseases, VPA possibly possesses distinct neurochemical and neurophysiological characteristics, resulting in a wide spectrum of actions against seizures and neurological diseases. However, the possible occurrence of serious side effects, teratogenesis, and liver toxicity has prompted a search for newer AEDs with better efficacy and fewer side effects.

LEV, the α-ethyl analog of piracetam, has linear pharmacokinetics, minimal protein binding, and a rapid onset of action, and it is completely excreted by the kidneys without any hepatic metabolism. LEV does not interact with other drugs, and it can be administered intravenously or orally twice a day[51], making it safe and effective in the treatment of patients with epilepsy, including those with partial seizures, resistant partial seizures, or other coexisting medical conditions[52]. LEV is proposed to have several modes of action, such as suppression of negative allosteric modulators of neuronal GABA- and glycine-gated currents, inhibition of voltage-gated calcium channels, reduction of voltage-operated potassium currents, and binding to synaptic vesicle protein 2A[52-55], but the exact mechanism of action is unknown. The effects of LEV on bone mass, biomechanical strength, and bone turnover are controversial. For instance, animal studies found that low-dose LEV in skeletally immature rats may affect longitudinal skeletal growth and fracture risk. LEV may impair the strength of the femoral neck by altering the bone microstructure/architecture. LEV was revealed to affect serum estradiol levels in the same rats, suggesting that long-term use of this drug

New-generation AEDs

LEV

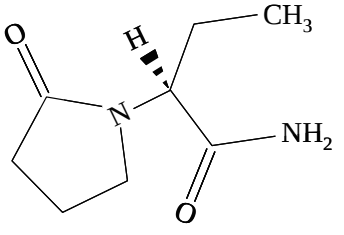

Fig. 6 Structural formula of levetiracetam.

might increase fracture risk in particularly young and female individuals drug[56]. However, several reports did not observe these adverse effects of LEV[54, 57, 58].

OXC is a structural derivative of CBZ with a ketone in place of the carbon-carbon double bond on the dibenzazepine ring at the 10 position (10-keto). OXC is approved as an adjunctive therapy or monotherapy for the treatment of partial seizures in adults and children. The mechanism of action of OXC is similar to that of CBZ, and it has comparable efficacy but superior safety to its parent drug according to controlled clinical trials[19, 59]. The structural differences may explain the low incidence of CBZ-related allergic reactions, enzyme-induced reactions, anemia, or agranulocytosis. Following oral administration, OXC is rapidly and almost completely metabolized to its monohydroxy derivative (MHD). OXC and MHD both have potent anticonvulsive properties, which are possibly mediated through their effects on neuronal ion fluxes, specifically blockade of voltage-dependent sodium, potassium, and calcium channels[19, 59]. The most common adverse effects of OXC include fatigue, drowsiness, diplopia, dizziness, nausea, vomit, skin rash, and hyponatremia[60]. Two studies reported that decreased BMD was detected in patients on long-term OXC therapy[61, 62]. OXC, which induces CYPs, was found to reduce levels of 25OHD and bone turnover biomarkers, such as PTH and bone ALP, and directly affect osteoblast proliferation, leading to bone loss[23, 62, 63].

LTG is a triazine derivate that can inhibit presynaptic voltage-sensitive sodium channels; block L-, N-, and P-type calcium channels; and inhibit 5-hydroxytryptamine-3 receptors, thereby stabilizing neuronal membranes and inhibiting glutamate release at cortical projections in the ventral striatum limbic areas, consequently leading to reduced GABA levels. LTG can block sustained repetitive firing in cultured mouse spinal cord neurons. Because of these antiseizure advantages and its neuroprotective and antiglutamatergic effects, LTG is approved for the treatment of epilepsy, including simple partial, complex partial, and secondarily generalized seizures, and authorized as an adjuvant therapy for focal onset tonic–clonic, atypical absence, myoclonic seizures, Lennox-Gastaut syndrome (LGS), juvenile myoclonic epilepsy, infantile spasms, absence seizures, and Rett syndrome[64]. LTG is mainly metabolized by the liver, and it is generally well tolerated at its maintenance dose. Although LTG has a broad clinical spectrum of effects, it has several adverse effects, including headache, dizziness, sedation, nausea, insomnia, diplopia, and ataxia. Meanwhile, the incidence of diarrhea and tremor associated with the drug is significantly lower. LTG does not cause weight gain. The incidence of serious rash with LTG treatment was 0.1% in all studies, although the rash can potentially progress to lethal Stevens–Johnson syndrome. To date, reports regarding the adverse effects of LTG on bone diseases are sparse. Guo et al. reported that LTG might impair growth in

OXC

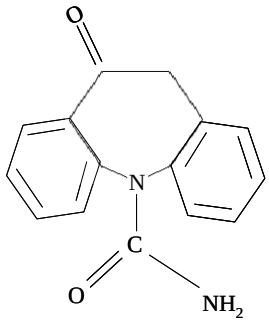

Fig. 7 Structural formula of oxcarbazepine.

LTG

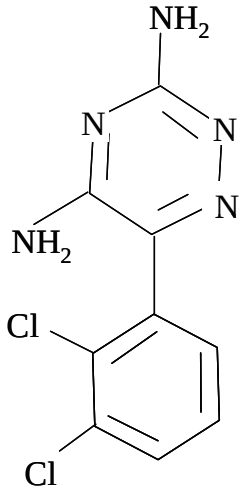

Fig. 8 Structural formula of lamotrigine.

TPM

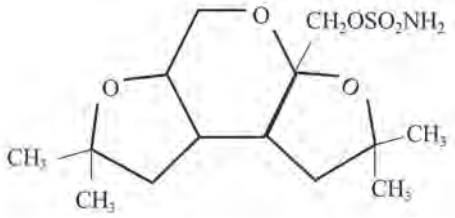

Fig. 9 Structural formula of topiramate.

children, decrease BMD, and elevate bone turnover markers[43], whereas several groups did not detect any osteopenic effects or significant alterations in bone metabolism in patients on long-term LTG therapy[21, 50, 65].

TPM is a sulfamate-substituted derivative of the monosaccharide D-fructose. Although the precise mechanisms of action are unknown, TPM enhances GABAergic activity, inhibits kainite/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid-type glutamate receptors and voltage-sensitive sodium and calcium channels, and prevents protein kinases from phosphorylating the channels. Based on these antiseizure properties, TPM is effective as a monotherapy or adjunctive therapy for patients with primary generalized tonic–clonic seizures, partial seizures or seizures associated with LGS[66]. TPM is also useful in the treatment of bipolar disorder, neuropathic pain, depression, obesity, alcoholism, and post-traumatic stress disorder and the prophylaxis of migraine. The common adverse effects of the drug include somnolence, hypo- or an-hydrosis, paresthesia, nystagmus, problems with concentration and word finding, decreased appetite, weight loss, metabolic acidosis, glaucoma, and nephrolithiasis[66, 67]. TPM is a carbonic anhydrase inhibitor). Excessive carbonic anhydrase inhibition may disturb bone metabolism and cause osteomalacia through metabolic acidosis, reducing PTH secretion, impairing the synthesis of 1,25(OH)2D, causing hypocalcemia, and attenuating the activities of osteoclasts[68]. Paradoxically, patients treated with TPM in our previous study did not exhibit significant hypocalcemia[50]. We hypothesized that lower doses of TPM might not disturb the in vivo acid-base homeostasis and the levels of PTH and 1,25(OH)2D, resulting in a subtle change of serum calcium levels.

GBP, a structural analog of GABA, is completely soluble in water and excreted in the urine and feces, but it is not metabolized by the liver. GBP can freely cross the blood–brain barrier, but it does not induce or inhibit hepatic enzymes. GBP is indicated as an adjunctive AED for the treatment of partial seizure with or without secondary generalization in patients older than 12 years and for a variety of pains, including postoperative pain, post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome, inflammatory pain, central pain, malignant pain, trigeminal neuralgia, HIV-related neuropathy, and headaches. The mechanisms of action of GBP are complicated. GBP may have an inhibitory effect on voltage-gated calcium channels containing the alpha 2-delta subunit instead of binding to GABA receptors in the central nervous system[69]. GBP may have side effects, including sexual dysfunction and weight gain. The relationship between GBP and bone diseases is not clear. Long-term GBP therapy is proposed to cause bone loss at the hips and lumbar spine[6, 16], and a prospective study concluded that GBP caused significant bone loss in the hips of older men[8], suggesting that it is necessary to closely monitor bone status in patients receiving GBP for epilepsy.

VGB is a GABA-aminotransferase inhibitor that decreases the synaptic breakdown of GABA. VGB is the first-line treatment for infantile spasms secondary to tuberous sclerosis because it is not metabolized by the liver[13]. It is also potentially effective as an initial monotherapy for untreated pediatric partial-onset seizures, LGS, and refractory complex partial seizures in patients with inadequate response to several alternative treatments. Fatigue, headache, dizziness, ataxia, tremor, weight gain, and hyperactivity are commonly noted. However, the drug may aggravate myoclonic seizure and cause serious side effects, such as visual field damage. Periodic ophthalmological examinations are recommended[70]. Although a previous study did not identify significant effects of AEDs, including LTG, TPM, GBP, and VGB, on BMD and bone mineral metabolism[65], VGB was found to decrease body mass gain and inhibit compact bone growth in immature rats[71]. Therefore, VGB should be used with caution. There is no convincing data regarding the relationship between VGB and bone turnover.

GBP

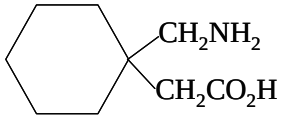

Fig. 10 Structural formula of gabapentin.

VGB

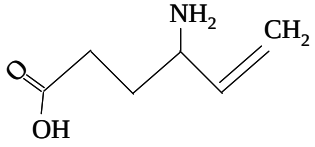

Fig. 11 Structural formula of vigabatrin.

Conclusion

Without doubt, AEDs are effective in the treatment of epilepsy. Approximately 50% of patients with newly diagnosed epilepsy become seizure-free after adequate AED treatment. However, bony pathological manifestations, abnormalities in bone and mineral metabolism, and decreased BMD have been commonly reported in individuals treated with classical (BZD, CBZ, PHT, PB, VPA) and/or with newer AEDs (LEV, OXC, LTG, TPM, GBP, VGB). Several mechanisms for AED-associated bone disease have been proposed. Some, but not all, studies proposed that AEDs negatively influence bone health, which was linked to CYP induction, resulting in reduced vitamin D levels and consequently impaired bone growth and calcium metabolism. To date, no single mechanism has successfully addressed all of the reported findings, and no definitive guidelines have been established for evaluation or treatment regarding these adverse effects of AEDs on impaired bone and calcium metabolism. Recent studies suggested that the broad-spectrum effects of AEDs on bone may be multifactorial and potentially injurious. Nevertheless, these results raise serious concerns regarding the bone health of patients who receive AEDs for epilepsy, and a 3–6-month monitoring schedule, prophylactic vitamin D supplementation, sufficient intake of dietary calcium, and weight-bearing exercise are recommended for all patients with epilepsy on initiation of AED therapy.

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抗癲癇藥物與骨骼健康的關聯性

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摘要

骨骼和鈣代謝疾患是治療兒童癲癇患者的主要問題之一，因為在此階段中，兒童會受到多種荷爾蒙的作用，而有快速生長，體重增加，骨骼和生殖器的成熟。然而在癲癇，抗癲癇藥物，骨骼和鈣平衡之間的關係是相對複雜和多方面。典型的抗癲癇藥物（例如 benzodiazepines, carbamazepine, phenytoin, phenobarbital, 和 valproic acid）或更新的抗癲癇藥物（例如 Levetiracetam, oxcarbazepine lamotrigine, topiramate, gabapentin, 和 vigabatrin）已被報導會對骨骼健康產生不利影響。抗癲癇藥物的另一特性，是細胞色素 P450（CYP-450）同功酶的誘導劑，可能導致維生素 D 的缺乏，鈣的濃度降低，骨量減少，骨折風險增加和改變骨代謝。由於這些抗癲癇藥物有廣泛的抗癲癇作用，涵蓋多種不同的作用機制，造成爭議的結果，這些都將在本文中討論。

關鍵詞：骨骼、鈣代謝、癲癇、a 抗癲癇藥物、細胞色素 P450

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