INTRODUCTION

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. An epileptic seizure is a transient occurrence of signs and /or symptoms due to abnormal excessive or synchronous neuronal activity in the brain ***(Fisher et al., 2014).***

Antiepileptic drugs (AEDs) are potentially an effective treatment for patients with epilepsy. The goal of AEDs is to suppress the rapid and excessive firing of neurons that start a seizure offering protection against possible excitotoxic effects that may result in brain damage. Although the actions of each antiseizure drug have unique characteristics and some drugs may act by multiple mechanisms, the anticonvulsant actions of drugs can be conveniently grouped into four broad categories:

1. Modulation of voltage dependent sodium, calcium or potassium channels.
2. Alterations in GABAergic inhibition via actions on GABAA receptors or on GABA synthesis, reuptake, or degradation.
3. Decreased synaptic excitation via actions on ionotropic glutamate receptors.
4. Modulation of neurotransmitter release via presynaptic mechanisms with an action on glutamate release being most relevant.

(Porter et al., 2012)

Most patients with epilepsy require long-term, and sometimes lifelong, therapy with antiepileptic drugs (AEDs). AEDs are associated with significant side effects including, radiological evidence of rickets, decreased bone mineral density (BMD), altered bone turnover, and increased risk of fracture ***(Zhang et al., 2015).***

Bone health may be assessed in several ways, through measures of:

1. Bone density (mainly assessed as density of calcified matrix).
2. Bone growth and size.
3. Biochemical measures of bone turnover and calcitropic hormones.

(Vestergaard, 2015)

The most widely accepted technique for measuring bone density is dual energy X-ray absorptiometry (DXA scan). As regarding biochemical measures of bone turnover, The most important, prevalent, cited and applicable bone resorption biomarker is C-terminal telopeptide of type 1 collagen (CTX) showing the highest correlation with the dynamics of bone ***(Cabral et al., 2016).***

AIM OF THE WORK

The aim of the present study is to investigate the effects of antiepileptic drugs on bone mineral density and bone turnover markers.

EPILEPSY

Definition:

Epilepsy, from the Greek epilepsia (a taking hold of or seizing), is a chronic disorder characterized by a spontaneous tendency for recurrent seizures. Seizures are the clinical manifestation of abnormally hyperexcitable cortical neurons ***(Foldvary-Schaefer and Wyllie, 2007).***

Epilepsy is one of the most common chronic neurologic disorders diagnosed in children and adolescents, the vast majority of epilepsies encountered under the age of 15 years are idiopathic, developing without any identifiable or suspected cause**,** other than a genetic predisposition in many cases ***(Dragoumi et al., 2013).***

Incidence and Epidemiology:

Human being has been aware of the presence of epilepsy for at least 2500 years; references from Egyptian, Babylonian, and Greek have identified this illness reliably. However there is great agreement on the veracity of references of epilepsy in Greek literatures in the fifth century BC ***(Temkin, 1945).***

Epilepsy is one of the most common and widespread neurological disorders, around 50 million people worldwide have epilepsy with nearly 90% of them are found in developing countries ***(WHO, 2009).*** In developed countries the incidence

of epilepsy varies between 50 and 100 per 100, 000 persons per year ***(Kobau and Price, 2009).***

In an Egyptian study conducted by ***Mekky et al. (1981)*** on El-Gabal El-Asfar population, the prevalence rate for epileptic seizures was 4.1 per 1000 population, with highest prevalence rate in the age group 10-19 years where it reached 7.4 per 1000. ***El-Afify and Mostafa (1981)*** detected a higher prevalence rate which was 9.87 per 1000 while ***El-Khayat et al. (1994)*** detected a prevalence rate which was 3.5 per 1000.

The prevalence of epilepsy is found to be higher in the lower socioeconomic groups ***(Bell and Sander, 2001)*** and those living in poverty ***(Elliott et al., 2009).***

It is estimated that 0.5-1% of all children have epilepsy, most of them presenting during infancy or early childhood ***(Ottman, 2001).***

Freitag et al. (2001), found that males are more affected than females, and suggested that females might find it easier to conceal their fits.

Pathophysiology:

Seizures are paroxysmal manifestations of the electrical properties of the cerebral cortex. A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons in favor of a sudden-onset net excitation ***(Fishers et al., 2005).***

Mechanisms leading to decreased inhibition

Mechanisms leading to decreased inhibition include defective gamma-aminobutyric acid (GABA)-A inhibition, defective GABA-B inhibition, defective activation of GABA neurons, and defective intracellular buffering of calcium ***(Najm et al., 2001).***

Mechanisms leading to increased excitation

These include increased activation of NMDA receptors, increased synchrony between neurons and increased activation due to recurrent excitatory collaterals ***(Najm et al., 2001).***

One interesting finding in animals is that repeated low-level electrical stimulation to some brain sites can lead to permanent increases in seizure susceptibility: in other words, a permanent decrease in seizure "threshold." This phenomenon, known as kindling ***(Morimoto et al., 2004).***

Mutations in several genes have been linked to some types of epilepsy. Several genes that code for protein subunits of voltage-gated and ligand-gated ion channels have been associated with forms of generalized epilepsy and infantile seizure syndromes. One speculated mechanism for some forms of inherited epilepsy are mutations of the genes which code for sodium channel proteins; these defective sodium channels stay open for too long thus making the neuron hyper-excitable. Glutamate, an excitatory neurotransmitter, may thereby be

released from these neurons in large amounts which by binding with nearby glutamanergic neurons triggers excessive Ca^{++} release in these post-synaptic cells. Such excessive calcium release can be neurotoxic to the affected cell. The hippocampus, which contains a large volume of just such glutamanergic neurons (and NMDA receptors, which are permeable to Ca^{++} entry after binding of both sodium and glutamate), is especially vulnerable to epileptic seizure, subsequent spread of excitation, and possible neuronal death. Another possible mechanism involves mutations leading to ineffective GABA (the brain's most common inhibitory neurotransmitter) action. Epilepsy-related mutations in some non-ion channel genes have also been identified ***(Hahn and Neubauer, 2009).***

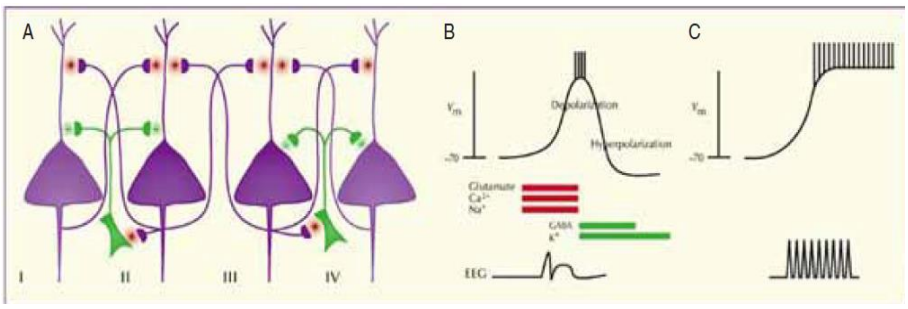

Figure (1): Paroxysmal depolarization shift (PDS). When a PDS occurs as an abnormally prolonged run of action potentials during sustained membrane depolarization is a single neuron, as shown in the upper trace in B, the event is detectable only with microelectrodes; increased glutamate concentration is associated with influx of cations initially, followed by increased GABA concentration with efflux of potassium. When PDSs in a large number of neurons are synchronized for less than 200 ms, as shown in A, these electrical potentials may summate as a spike-wave complex that is recorded with microelectrodes, as shown in the lower trace in B. When sustained repetitive firing of PDSs in a large number of neurons becomes synchronized for many seconds or longer, an electrographic seizure occurs, as shown in C ***(Holmes and Ben-Ari, 2003).***

Figure (1) shows The paroxysmal depolarization shift **(PDS)** phenomena which is the pathophysiological cellular

phenomenon that underlies all types of epileptic seizures and interictal epileptiform electroencephalography (EEG) abnormalities ("spikes") where There is disruption in cellular events in which rapidly repetitive action potentials are not followed by the usual refractory period, thereby generating a prolonged membrane depolarization (which is more prolonged than typically occuring in response to normal excitatory postsynaptic potentials **[EPSPs]**) ***(Holmes and Ben-Ari, 2003).***

The tendency of individual neurons to enter pathological states in which PDSs are generated can be based on intrinsic neuronal properties, such as dysfunctional ionophores in the genetically determined channelopathies (**Figure 2**), or on extrinsic mechanisms such as inadequate inhibitory neurotransmitter concentrations or exposure to excessive concentrations of excitatory amino acids or exogenous excitotoxins. However, large groups of neurons must generate PDSs simultaneously to account for the episodic nature of seizures ***(Chang and Lowenstein, 2003)***.

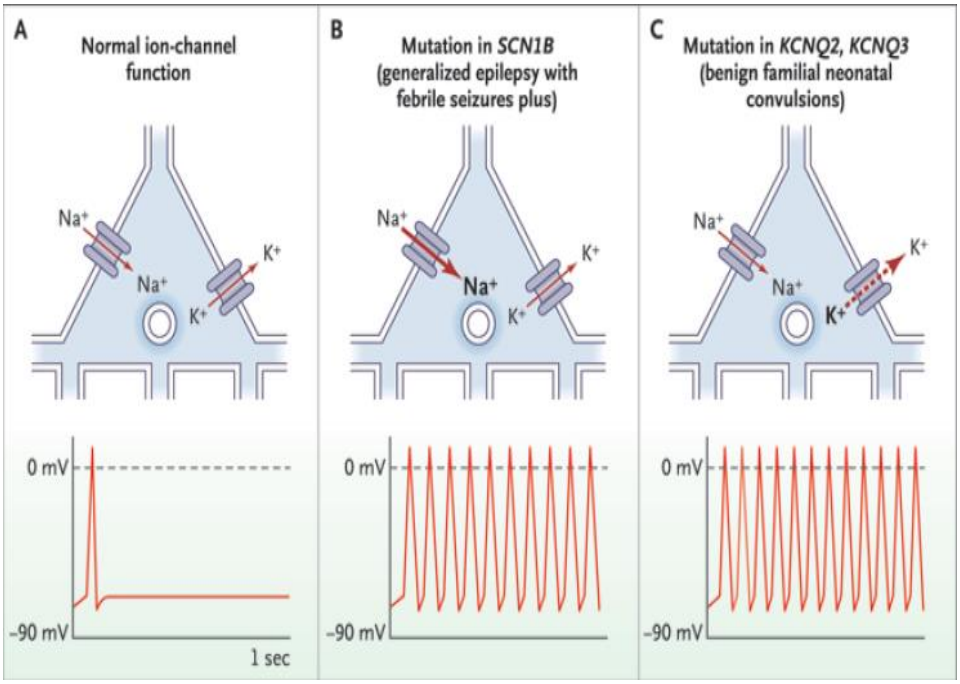

Figure (2): Genetic channelopathies in epilepsy. (A) Genetic channelsopathies can support the occurrence of paroxysmal depolarization shifts (PDS) by altering the usual balance of Na+ and K+ ion conductance across neuronal membranes. Increased Na+ conductance (B, upper panel) creates a situation in which a single action potential intiates sustained depolarization as a PDS (B, lower panel). Decreased K+ conductance (C, upper panel) also can predispose to PDS ***(Chang and Lowenstein, 2003).***

In experimental models of generalized epilepsies, this widespread epileptic synchronization of interictal and ictal PDSs is based on intrathalamic synchronization that drives thalamocortical relay neurons to synchronize the bihemispheric cortical neuronal discharges (**Figure 3**). In experimental models of partial epilepsies, intracortical mechanisms of synchronization operate during ictal discharges ***(Chang and Lowenstein, 2003)***.

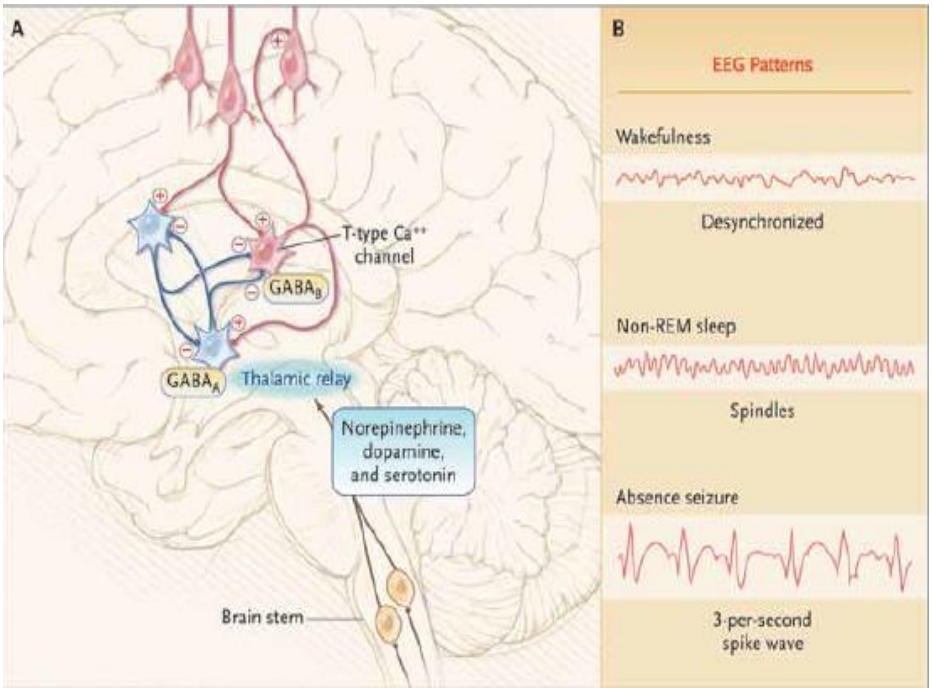

Figure (3): Thalamocorticla circuits in generalized epilepsies. Under normal conditions, brainstem monoaminergic projections synchronized the thalamic reticular neurons into cycles of slow waves, and GABAergic projections of these neurons synchronized thalmocortical relay neurons into cycles of slow waves, resulting in synchronized glutamatergic thalamocorticla projections of widespread cortical areas that generate the electroencephalgraphy (EEG)-recorded slow waves of non-REM sleep and also sleep spindles. In generalized epilepsies, repetitive paroxysmal depolarization shifts (PDSs) in thalamic retricualr neurons synchronize PDSs in thalamocrotical relay neurons, which in turn synchronize PDSs in cortical neurons, thus generating EEG-recorded spike-wave discharges and sometimes absence seizures. Presumably, a structurally normal complement of thalamic and cortical neurons and their pathways are able to generate spike-wave discharges and absence seizures due to genetically based dysfunction of channels, receptors, or other uencorchemical elements ***(Chang and Lowenstein, 2003).***

The thalamocortical interaction is the best-understood example of the pathophysiologic mechanisms of generalized seizures that may underlie typical absence seizures. The

thalamocortical circuit has normal oscillatory rhythms, with periods of relatively increased excitation and periods of relatively increased inhibition. The circuitry includes the pyramidal neurons of the neocortex, the thalamic relay neurons, and the neurons in the nucleus reticularis of the thalamus (NRT). Altered thalamocortical rhythms may result in primarily generalized-onset seizures. The thalamic relay neurons receive ascending inputs from spinal cord and project to the neocortical pyramidal neurons. Cholinergic pathways from the forebrain and the ascending serotonergic, noradrenergic, and cholinergic brainstem pathways prominently regulate this circuitry ***(McCormick, 1992).***

The thalamic relay neurons can have oscillations in the resting membrane potential, which increases the probability of synchronous activation of the neocortical pyramidal neuron during depolarization and which significantly lowers the probability of neocortical activation during relative hyperpolarization. The key to these oscillations is the transient low-threshold calcium channel, also known as T-calcium current. In animal studies, inhibitory inputs from the NRT control the activity of thalamic relay neurons. NRT neurons are inhibitory and contain GABA as their main neurotransmitter. They regulate the activation of the T-calcium channels in thalamic relay neurons because those channels must be de-inactivated to open transitorily ***(Blumenfeld, 2003).*** T-calcium channels have 3 functional states: open, closed, and inactivated.

Calcium enters the cells when the T-calcium channels are open. Immediately after closing, the channel cannot open again until it reaches a state of inactivation. The thalamic relay neurons have GABA-B receptors in the cell body and receive tonic activation by GABA release from the NRT projection to the thalamic relay neuron. The result is a hyperpolarization that switches the T-calcium channels away from the inactive state, permitting the synchronous opening of a large population of the T-calcium channels every 100 milliseconds ***(Khosravani and Zamponi, 2006).***

Etiology:

In about 60% of diagnosed epileptics, no reasonable cause for seizure is found, and the condition is referred to as idiopathic ***(Nordli et al., 2003).***

Epilepsy has a wide range of causes and indeed almost all grey matter diseases can result in seizures and the most important factor influencing the range of causes is age ***(Kobayashi et al., 2006)***.

Genetic aspect of epilepsy:

Genetics have for long time been suspected of playing an important role in idiopathic generalized epilepsy. The last decade has seen the discovery of several genes underlying epilepsy transmitted in Mendelian fashion. These are genes

causing recessive neuro-developmental disorders complicated by seizures ***(Kullmann, 2003).***

For most types of seizures, polygenic or multifactorial factors exist. Only a small number of seizures disorders are inherited as autosomal, or very rarly X linked traits, sibilings and off springs of persons with seizure disorders have an increased risk is, approximately l-l 0% ***(Seashore and Wappner, 1996).***

Different mutations in genes that control the excitability of neurons have been described in childhood epilepsies ***(Lagae, 2008).***

Only a few "monogenic epilepsies" were clearly identifies, but the underlying genetic mechanisms involved were found to affect major pathophysiological pathways in the brain. The large majority of the genes involved are regulating excitation and inhibition at the neuronal and the synaptic levels. The major players involved are the potassium, sodium, GABA receptor and chloride channelopathies ***(Heron and Scheffer, 2007).***

Idiopathic generalized epilepsies have complex inheritance associated with the interaction of two or more genes. Sporadic cases are common and affected families are usually small. Close relatives of probands have a 4-10 % risk of developing epilepsy which is highest in sibiling and offspring

than in other relatives. There is higher concordance for idiopathic generalized epilepsies in monozygotic than dizygotic twins (0.76 vs 0.33) ***(Guerrini, 2006).***

Classification of epileptic seizures & epileptic syndromes

Classification system provides a logical, organized approach and gives a universal language shared among health professionals all over the world. The International League against Epilepsy (ILAE) Classification of epileptic Seizures 1981 divides seizures into 2 major classes: partial-onset seizures and generalized-onset seizures. Partial-onset seizures begin in a focal area of the cerebral cortex, whereas generalized-onset seizures have an onset recorded simultaneously in both cerebral hemispheres. Some seizures are difficult to fit into a single class, and they are considered unclassified seizures. This classification is based on observation (clinical and EEG) rather than the underlying pathophysiology or anatomy ***(Commission on classification and terminology of the ILAE, 1981).***

With the increasing description of reasonably well defined epilepsies, the ILAE made its first attempt to organize them into a coherent classification in 1985 and was revised in 1989. It divides epilepsy syndromes by location or distribution of seizures (as revealed by the appearance of the seizures and by EEG) and by cause. Syndromes are divided into

localization-related epilepsies, generalized epilepsies, or epilepsies of unknown localization as shown in table 1 ***(Commission on classification and terminology of the ILAE, 1985 and 1989)***.

Generalized epilepsies arise from many independent foci (multifocal epilepsies) or from epileptic circuits that involve the whole brain. Epilepsies of unknown localization remain unclear whether they arise from apportion of the brain or from more wide spread circuits, in contrast, Localization-related epilepsies, sometimes termed partial or focal epilepsies, arise from an epileptic focus, a small portion of the brain that serves as the irritant driving the epileptic response ***(Commission on classification and terminology of the ILAE, 1989).***

Epilepsy syndromes are further divided by presumptive cause: idiopathic, symptomatic, and cryptogenic. Idiopathic epilepsies are generally thought to arise from genetic abnormalities that lead to alteration of basic neuronal regulation. Symptomatic epilepsies arise from the effects of an focal epileptic lesion or a defect in metabolism causing widespread injury to the brain. Cryptogenic epilepsies involve a presumptive lesion that is otherwise difficult or impossible to uncover during evaluation ***(Commission on classification and terminology of the ILAE, 1989).***

The International League against Epilepsy (ILAE) Commission on Classification and Terminology has revised