International Journal for Innovative Engineering and Management Research
PEER REVIEWED OPEN ACCESS INTERNATIONAL JOURNAL
www.ijiemr.org

A STUDY OF DIAGNOSIS AND MEASURING THE OUTCOME TREATMENT OF EPILEPSY

CANDIDATE NAME = LOKHANDE RAHUL PRAKASH
DESIGNATION – RESEARCH SCHOLAR MONAD UNIVERSITY HAPUR U.P
GUIDE NAME = DR. NARENDRA SINGH
DESIGNATION= PROFESSOR MONAD UNIVERSITY HAPUR U.P

ABSTRACT

The reaction of acetophenone with substituted aldehydes is a suitable strategy for the synthesis of numerous benzothiazepine derivatives. The acetophenone scaffold is the foundation of the benzothiazepine scaffold. However, aldehydes that have been "substituted" allow for the introduction of new functional groups and substituents, allowing the pharmacological profile to be fine-tuned. The significance of this study is driven by the current dearth of effective and selective anticonvulsant medicines. Producing and screening a library of 1,5-benzothiazepine derivatives to examine the structure-activity relationship (SAR) can lead to the discovery of compounds with improved anticonvulsant effect. The insights gathered from this study into the mechanisms of action of these compounds will help in the development of more effective anticonvulsant drugs. The simplicity and effectiveness of the synthetic approach make it possible to synthesize on a large scale, which will be essential for future preclinical and clinical studies. The ability to synthesis these compounds in sufficient numbers enables thorough in vitro and in vivo studies, including pharmacokinetic and toxicological research, expanding our understanding of their potential as anticonvulsant medicines.

KEYWORDS:- benzothiazepine derivatives, acetophenone scaffold, pharmacological profile, anticonvulsant medicines, 1,5-benzothiazepine derivatives

INTRODUCTION

The 1, 5-benzothiazepines are crucial seven-membered heterocyclic molecules containing nitrogen and sulfur. Most people are familiar with 1, 5-benzothiazepines, which are just one of three potential benzo-condensed derivatives of 1, 4-thiazepine.

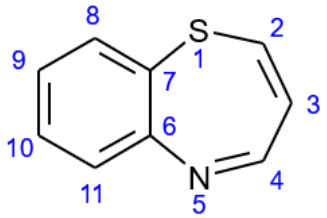
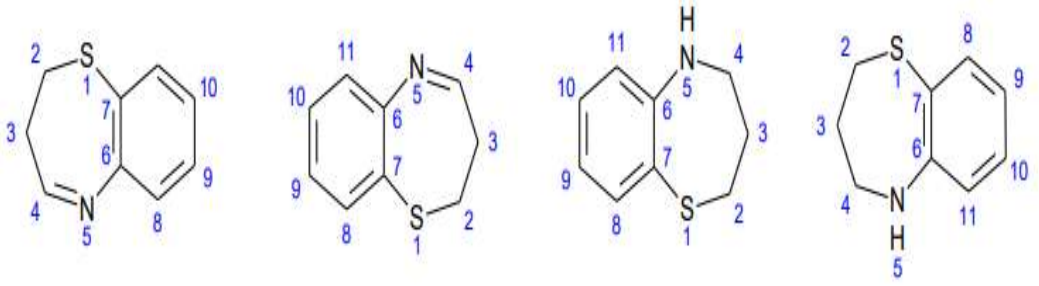


Figure 2 Structure of Benzothiazepines Nomenclature and Way of Numbering

1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine. According to the IUPAC nomenclature, the benzo[1, 5]thiazepine structures **IA** or **IB** may be named as (*Z*)-2,3-dihydrobenzo[*b*][1,4]thiazepine or (*Z*)- 2,3dihydro-substituted-

International Journal for Innovative Engineering and Management Research
PEER REVIEWED OPEN ACCESS INTERNATIONAL JOURNAL
www.ijiemr.org

benzo[*b*][1,4] thiazepine. Also, the substituted- benzo[1,5] thiazepinesstructure **IIA** or **IIB** may have the name: 2,3,4,5- tetrahydrobenzo[*b*][1, 4]thiazepine or 2,3,4,5-tetrahydro-substituted benzo[*b*][1, 4]thiazepine [41]



IA IB IIA IIB

Biological aspects of 1,5-benzothiazepines

Because of their activity against many target families, 1,5-benzothiazepine derivatives are a promising class for future lead discovery. Clinical usage of 1, 5-benzothiazepine molecules for their cardiovascular effects began with diltiazem and has now expanded to include clentiazem. Thiazesim, Clothiapine, and quetiapine are only a few of the 1, 5-benzothiazepine derivatives that have seen therapeutic usage for the treatment of CNS diseases. The 1, 5-benzothiazepine moiety is typically synthesized by reacting 1, 3-diarylprop-2-enones with o-aminothiophenol. Microwave irradiation of inorganic solid supports like alumina, silica gel, and clay, as well as the use of acetic acid or trifluoroacetic acid, hydrochloric acid, piperidine, etc., are only some of the methods mentioned. One of the three benzocondensed derivatives, along with 1,4- and 1,5-benzothiazepine, is known as 1,5-benzothiazepine. There is a lack of information in the literature on the pharmacological effects of the parent 1, 5-benzothiazepine, 1. Its analogues, however, are among the most investigated moieties. Because of their activity against many target families, 1, 5-benzothiazepine derivatives are a promising class for future lead discovery. Vasodilators, antiarrhythmics, inhibitors of proteases and elastases and angiotensin converting enzyme, antagonists of several G-protein coupled receptors including the cholecystokinin (CCK) receptor, and ACE inhibitors are all built on the 1, 5-benzothiazepine scaffold.

Spasmolytic, antiulcer, and anticancer actions, as well as hemodynamic effects, have been documented more recently. Diltiazem was the first chemical to be utilized therapeutically for its cardiovascular effect, followed by clentiazem. Clinical usage of 1,5- benzothiazepine derivatives, such as thiazesim and quetiapine fumarate, has also been documented for the treatment of central nervous system (CNS) problems. Preclinical research is being conducted on two derivatives, 7-bromo-3(S)-butyl-3-ethyl-8-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1,1-benzothiazepine-dioxide (GW577) and 5-[N-[2-(3,4-dimethoxypheny)-ethyl]-b-alanyl], for the treatment of lipoprotein disorders and inhibition of the transportThe antihypertensive,

antiarrhythmic, calcium channel antagonist action of 2,3,4,5-tetrahydro-1,5-benzothiazepine (KT- 363) is now being tested in phase II clinical studies.

Only one member of the CCB benzothiazepine subclass, diltiazem, is currently in clinical use. The binding of diltiazem to amino acid residues in segments IIIS6 and IVS6 prevents VGCC from functioning. Some of these amino acids have a role in DHP and PAA binding, but not all of them do. Although both verapamil and diltiazem can affect DHP binding, they do not compete with one another for binding. While verapamil's use- and frequency-dependent VGCC inhibition is more pronounced, diltiazem's use-dependence is less pronounced, and its cardiodepressant effects are less pronounced. Diltiazem reduces blood pressure by relaxing blood vessels, despite the fact that it also has cardiodepressant effects.

DIAGNOSIS OF EPILEPSY

Commonly mistaken as epileptic seizures are syncopal attacks, one of the diseases listed in Table no. 1 that can mimic epileptic seizures. In addition, non-epileptic episodes sometimes coexist with epilepsy or may arise as a substitute for seizures after the epilepsy is managed, making the diagnosis of pseudo seizures or non-epileptic psychogenic seizures challenging (10-45% of patients with seemingly intractable epilepsy). An accurate diagnosis of epilepsy is crucial for establishing a likely prognosis and choosing the best course of therapy. Clinical examination and testing are the two main components of an epilepsy diagnosis.

It's unusual for a patient to experience a seizure during a checkup. In addition, some forms of seizures might cause the patient to lose consciousness, making it impossible for them to offer a detailed account of the symptoms they encountered. Therefore, it is necessary to gather a thorough history from the patient and any witnesses who may have seen the seizures. Trevavathan demonstrated that, prior to doing any investigations; a true diagnosis of epilepsy could be made in 96% of instances simply by taking a complete history from patients. Differentiating between epileptic and nonepileptic seizures is crucial in this context, since the list of differential diagnoses of seizure is extensive (Table number 1).

In order to discover any neurological deficiency that correlates to an underlying ailment in the brain, a thorough physical and neurological examination is often undertaken. On the other hand, insufficient history taking and a failure to detect a differential diagnosis were highlighted as major reasons why almost one-quarter of epilepsy patients in some clinics in the industrialized world were proven not to have the condition.

Research on epilepsy is used to corroborate a clinical diagnosis, determine the type of seizures a patient is experiencing, and identify any underlying brain abnormalities.

Because of its capacity to detect and categorize epileptiform EEG activity, electroencephalography (EEG) plays a crucial role in the epilepsy diagnostic process. The placement and lateralization of epileptogenic EEG foci can provide an explanation for some of the clinical symptoms, such as aura, through an EEG reading. Epilepsy is diagnosed by

monitoring abnormal and occasionally recognizable patterns of electrical discharge in the brain.

In 1984, magnetic resonance imaging (MRI) entered clinical use as yet another crucial technique in the diagnosis of epilepsy. It is the epilepsy structural neuroimaging method with the highest sensitivity and specificity. It helps find the brain lesion at the root of the epileptic symptomatology. Hippocampal sclerosis, cortical development anomalies, vascular malformations, tumors, and acquired cortical injury are the most prevalent abnormalities detectable by MRI. Symptomatic epilepsy and complicated partial seizures are two of the best candidates for MRI treatment. When a patient has metal aneurysm clips, a cardiac pacemaker, severe claustrophobia, an urgent cerebral hemorrhage, or a skull fracture, a CT scan is preferable over an MRI. Epilepsy evaluation now also makes use of a number of additional functional imaging of the brain approaches. Examples of this kind of imaging technology are single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and functional magnetic resonance imaging (MRI).

Table 1. Common differential diagnosis in epilepsy

Disorder	Description
Neurological disorders	Transient ischemic attack
	Transient global amnesia
	Migraine
	Narcolepsy
	Panic attacks
Cardiac disorders	Vasovagal syncope
	Reflex anoxic seizure
	Sick sinus syndrome
	Arrythmias
	Hypotension
Endocrine/ metabolic Disorders	Hypoglycemia
	Hyopnatremia
	Hypkalemia
Paroxysmal movement disorders	Acute dystonic reactions

	Hemifacial spasm
	Non-epileptic myoclonus
Psychological	Non-epileptic psychogenic seizures

A wrong diagnosis of epilepsy can have devastating effects. Among these is the administration of unsuitable care to patients who lack adequate supervision. Other repercussions include the emotional toll of an epilepsy diagnosis, as well as economic setbacks in areas such as driving privileges, schooling, job, and insurance. Serious side effects and the possibility of teratogenicity in women of reproductive age are among the negative outcomes associated with AEDs.

MEASURING THE OUTCOME OF EPILEPSY

Using a wide range of data sources and quantifiable indicators, outcomes research evaluates the quality of medical treatment provided to patients. Several tools can be employed for various goals in the study of epilepsy. The frequency and intensity of seizures, as well as their influence on physical and social functioning, the effectiveness of drug treatment, the outcomes of surgical intervention, and the overall impact of epilepsy and treatment on patients' quality of life (QOL) are all quantifiable.

It has been challenging and illusive to develop reliable methods for measuring outcome in epilepsy and establishing the efficacy of an AED. Reasons for this include the fact that randomized controlled trials of treatments for epilepsy are notoriously difficult to design and implement, as well as the absence of clear criteria on the minimum standards to be utilized to quantify epileptic outcomes. There were a total of 54 distinct metrics employed in the 44 randomized controlled trials of AEDs that were reported by Baker and colleagues. It will be difficult, if not impossible, to draw significant comparisons between these trials and learn anything valuable about the effects of these AEDs.

Using seizure frequency as an indication of epilepsy outcome is one such example where having a clear and precise measure of outcome is complicated by its practical use. According to the study of the Commission on Outcome Measurement in Epilepsy (COME), the frequency of seizures is the most sensitive indicator for determining the efficacy of AEDs. Researchers may get misleading information if they rely on seizure diaries patients have kept because some patients may not recognize genuine seizures events and others may have ulterior motives for censoring their disclosure, especially considering the impact on employment and driving privileges. Seizure data may be missing in some situations due to the length of time between clinic visits. One of the most common ways to estimate the frequency of seizures is with Engel's score.

TREATMENT OF EPILEPSY

In reality, the epilepsy therapy options available are quite restricted. Furthermore, the application of some of these choices remains a contentious subject. The cornerstone of treating epilepsy is antiepileptic medications (AEDs). AED medication is effective in treating seizures in about 60–70% of people with epilepsy.

Inhibition of carbonic anhydrase

Carbonic acid is produced when carbon dioxide and water are reacted by carbonic anhydrase. Carbonic anhydrase in the brain controls (through the Na+/K+ anion exchanger) the intracellular conversion of chloride ions to bicarbonate ions (HCO_3). The majority of the brain's carbonic anhydrase activity, or 97%, is carried out by carbonic anhydrase II. Acetazolamide is an antiepileptic drug (AED) that inhibits carbonic anhydrase, and this inhibition is responsible for the drug's established anticonvulsant activity.

When carbonic anhydrase is blocked or not enough of it is produced, carbon dioxide builds up in the brain, which has an anticonvulsant effect. Seizures produced by flurothyl and scPTZ are less common in carbonic anhydrase II deficient individuals. The buildup of carbon dioxide caused a decrease in pH, which in turn antagonized NMDA receptors. When animals, and especially mice with carbonic anhydrase II deficiency, experience severe systemic acidosis, NMDA receptor function and, by extension, anticonvulsant action, decreases.

Mechanisms of action of commonly prescribed AEDs Phenobarbital

In addition to phenobarbital, mephobarbital, metharbital, and primidone also make up the barbiturates. It is still utilized in therapeutic treatment, especially in the developing world, due to its low cost and high usability despite its adverse effects, which include cognitive (behavioral) alterations. Phenobarbital has several uses besides its primary one as an anticonvulsive medication, including those of an anesthetic and a sedative hypnotic.

Phenobarbital exerts its anticonvulsant effects by binding to a particular location of chloride channels in GABA-A receptors at postsynaptic terminals. This increases the inhibitory action of GABA. This binding lengthens the average duration that chloride channels are open without affecting their spontaneous activity. The net outcome is an increase in GABA system activation, resulting in a decrease in neuronal firing rate and seizure control.

High voltage activated calcium channels are also negatively impacted, but to a lesser extent. Phenobarbital's effects on voltage-gated sodium channels are consistent with its ability to reduce the frequency of action potential firing at high doses.

Epilepsy Treatment and Beyond: Synaptic Vesicle Glycoprotein 2A Ligands

International Journal for Innovative Engineering and Management Research
PEER REVIEWED OPEN ACCESS INTERNATIONAL JOURNAL
www.ijiemr.org

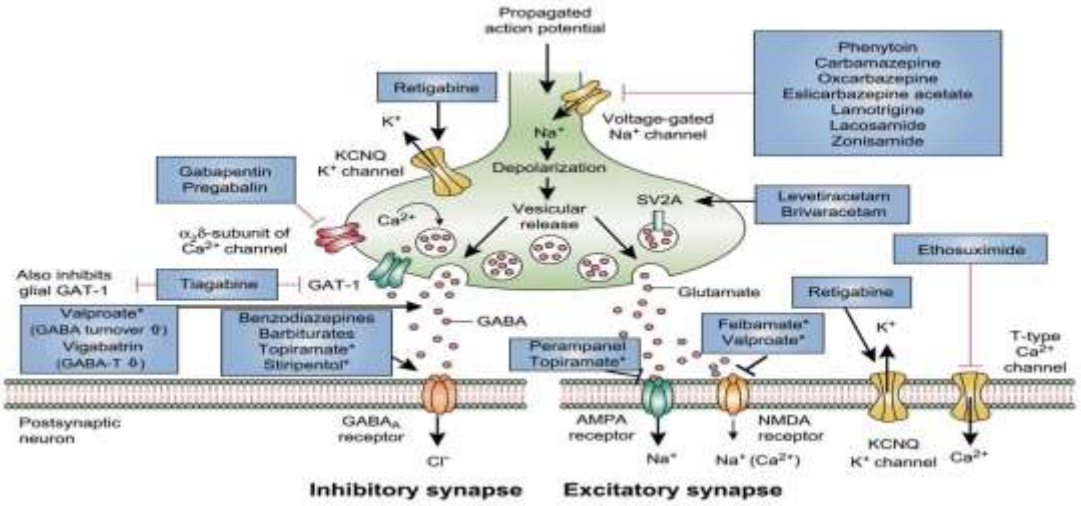


Figure 1 Target sites for Antiepileptic Drugs:[40]

Ion fluxes across the membrane are linked to the excitability of cells. A transitory refractoriness to stimulation is caused by an excess of sodium at the resting membrane potential, a phenomenon also known as after hyperpolarization.

Voltage-gated sodium channels:

Voltage-gated sodium channels play a crucial role in the action potential, as was described above. Voltage-gated sodium channels go through a variety of functional states in response to shifts in membrane potential. Within milliseconds of opening, sodium channels are rapidly inactivated by closing from the interior of the membrane. This inactivated state of the channel does not contribute to the excitability of neurons. Once the membrane is back to its resting potential, the sodium channel can be rapidly activated in response to further depolarization. This resting state is based on a separate mechanism inhibiting the ion channel. Slow inactivation is a different type of inactivation that takes place over a period of seconds to minutes and is triggered by circumstances of prolonged depolarization and recurrent activation patterns.

Voltage-gated calcium channels:

The gating of voltage-dependent calcium channels is regulated by a number of other subunits, including as the a 2d, b, and g subunits. The a1 subunits create the ion-conducting pore and house the voltage sensor. Because of their crucial modulatory role, auxiliary subunits have been shown to be promising targets for a 2d. Calcium channels may be broken down into two types, low-voltage activated and high-voltage activated, depending on the threshold at which they are activated. Bursting behavior and aberrant oscillations in thalamic sub regions during absence seizure activity are strongly contributed to by low-voltage activated T-type calcium channels. Since most antiepileptic medications that are effective against absence seizures interact with these ion channels, it is not unexpected that T-type

calcium channels are regarded a key target for therapy of these seizures. Subgroups of high-voltage activated calcium channels (L-, R-, P/Q-, and N-type) have been identified. Many members of this family are involved in neurotransmitter release, and their expression at presynaptic terminals provides a functional connection between the two processes. It's possible that excessive neurotransmitter release can be avoided if high-voltage-activated calcium channels are blocked. Several antiepileptic medicines interact with high-voltage activated calcium channels, adding another layer of complexity to their already multifaceted mode of action. Lamotrigine, felbamate, topiramate, levetiracetam, and phenobarbital are all part of this class of medications.

Potassium ions are present in relatively high quantities inside the cell, while calcium and chloride ions are distributed in the extracellular space. Only potassium ions are able to pass through the membrane at the resting potential. Channel opening facilitates a fast inflow of sodium ions, contributing to a further rise in membrane potential once it has crossed the threshold potential. After the electrochemical gradient has been reset, the membrane polarity is restored when sodium channels close and potassium channels are opened, resulting in a potassium current that flows outward. After the action potential, there is a brief depolarization that leads to a momentary resistance to excitation; this phenomenon is known as after- hyperpolarization.

Targeting of GABAergic neurotransmission:

Inhibitory neurotransmitter GABA is both prevalent and crucial. Changes in GABA receptor expression and subunit composition may lead to increased excitability in the epileptic brain. There are two types of receptors that GABA may interact with in the brain: postsynaptic GABAA receptors and pre- and postsynaptic GABAB receptors. Chloride influx into a neuron causes hyperpolarization and decreased excitability when inotropic GABAA receptors are activated in the adult brain. Depolarizing GABA responses may occur if the direction of chloride fluxes is reversed due to changes in the chloride concentration gradient that may be caused by illness. There is mounting evidence that alterations in the expression of the potassium/chloride co-transporter KCC2 can influence the transmembrane chloride gradient. However, the ligand's affinity for GABAA receptors with a varied subunit composition can also have qualitative effects on GABAA receptor activation. This is likely due to variations in brain function across different regions. The pentameric GABAA receptors are made up of five different subunits. With 19 subunits representing 5 distinct subunit families, there is a great deal of combinatorial freedom. The great majority of CNS receptors, however, consist of only two a, two b, and one g receptor subunits. Metabotropic G-protein coupled receptors like GABAB are a kind of ion channel. Adenylyl cyclase, voltage-gated calcium channels, and G-protein-coupled inwardly rectifying potassium channels are all targets of their activation. One of the earliest techniques in the pharmacotherapy of epilepsy was the manipulation of GABAergic neurotransmission. Bromides were initially used to treat epilepsy decades ago, and their mechanism of action—the increase of GABAA receptor mediated inhibition—was just recently discovered.

Bromides pass through GABAA receptor-associated ion channels more effectively than chloride ions, which are thought to be the cause of the action. Phenobarbital is another older antiepileptic medication that targets GABAergic signaling and, unlike bromides, is still widely used in many countries. Phenobarbital enhances GABA responses by binding to a particular location on the GABAA receptor complex (Macdonald and Olsen, 1994). Receptor receptive fields lengthening play a role in mediating the impact. Additionally, phenobarbital at high enough doses can directly activate GABAA receptors. This explains why the use of barbiturates has a higher risk of lethal overdose compared to other GABAA receptor agonists.

CONCLUSION

A few numbers indicate greater drug similarity within the acceptable range. The designed compounds have molecular weights between 311-450 dalton. Fifty designed compounds exhibited one Lipinski violation with pharmacological properties comparable to 90% of available medications with high to moderate oral bioavailability. If Lipinski violation is greater than one, there is an issue with oral bioavailability. All structures exhibited significant values for the analyzed properties, as well as drug-like characteristics based on the Lipinski rule of five. The ADMET values predicted for designed compounds are listed in. The compounds comply with Lipinski's rule of five for molecular weights less than 500 dalton, rotatable bonds less than 10, and the number of hydrogen bond donors and acceptors less than 5 and 10, respectively, with the exception of the partition coefficient between octanol and water (log P(o/w), which is found to be between 5 and 6).8.Blood Brain Barrier partition coefficient parameter indicates the drug's potential to cross the blood-brain barrier, which is required for GABA-ergic inhibition enhancement. Out of fifty designed compounds, A2, A3, A4, C202, C209, C210, and C226 exhibited anticonvulsant activity, and the compounds that displayed an acceptable range of descriptors can be assigned for future drug design. Predictability is the primary barrier to the ubiquitous use of in silico ADME-Tox methodologies. There are numerous programs for estimating the physicochemical properties of a compound, and many of them have existed for several years. For a successful application of ADME-Tox models, the paucity of sufficient chemical, physicochemical, and biochemical data for a comprehensive statistical evaluation is the most significant limitation. In spite of the fact that in silico models are not as accurate as in vitro or in vivo assays, the statistical results are compelling and consistent with the reality that approved drugs are less toxic than bioactive compounds. Using bio predictor software, fifty 1,5-benzothiazepine derivatives were analyzed computationally in an effort to identify potential lead molecules that may bind efficiently to the human GABA receptor. Our ADMET studies permit us to evaluate a set of anti-convulsion lead compounds and to access the parameter which will be essential for further lead optimization efforts.

REFERENCES

1. Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. Epilepsia. 2001; 42(06): 796-803.

2. Smith D, Defalla BA, Chadwick DW. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. Qjm-An International Journal of Medicine. 1999; 92(01): 15-23.

3. Devinsky O. Patients with refractory seizures. New England Journal of Medicine. 1999; 340: 1565-1570.

4. Trevathan E. The diagnosis of epilepsy and the art of listening. Neurology. 1996; 61(01): E13- E14.

5. Simkiss D. The diagnosis and management of epilepsy. Journal of Tropical Pediatrics 47: 320-321.

6. Oguni H. Diagnosis and treatment of epilepsy. Epilepsia. 2004; 45(08): 13-16.

7. Bergen D, Bleck T, Ramsey R, Clasen R, Ristanovic R, Smith M, Whisler WW. Magnetic-Resonance Imaging As A Sensitive and Specific Predictor of Neoplasms Removed for Intractable no Epilepsy. Epilepsia. 1989; 30: 318-321.

8. Duncan JS. Imaging and epilepsy. Brain. 1997; 120: 339-377.

9. Petkar S, Jackson M, Fitzpatrick A. Management of blackouts and misdiagnosis of epilepsy and falls. Clinical Medicine. 2005; 5: 514-520.

10. Chowdhury FA, Nashef L, Elwes RDC. Misdiagnosis in epilepsy: a review and recognition of diagnostic uncertainty. European Journal of Neurology. 2008; 15: 1034-1042.

11. Baker GA, Camfield C, Camfield P, Cramer JA, Elger CE, Johnson AL, da Silva AM, Meinardi H, Munari C, Perucca E, Thorbecke R. Commission on outcome measurement in epilepsy, 1994-1997: Final report. Epilepsia. 1998; 39: 213-231.

12. Baker GA, Hesdon B, Marson AG. Quality-of-life and behavioral outcome measures in randomized controlled trials of antiepileptic drugs: A systematic review of methodology and reporting standards. Epilepsia. 2000; 41(11): 13571363.

13. Engel J, Shewmon DA. Who should be considered a surgical candidate? Engel J. (Ed.) Surgical treatment of the epilepsies, 2 Ed. Raven Press, New York, pp. 23-34.

14. Mattson R, Cramer JA. Quantitative assessment of adverse drug effects. Meinardi

H., Cramer J.A., Baker G.A., da Silva A.M. (Eds.) Quantitative Assessment of Epilepsy Care. Plenum Press, New York, pp. 123-135.

15. Donoghue MF, Duncan JS, Sander JWAS. The National Hospital Seizure Severity Scale: A further development of the Chalfont Seizure Severity Scale. Epilepsia. 1996; 37(06): 563-571.

16. Kwan P, Brodie MJ. Early identification of refractory epilepsy. New England Journal of Medicine. 2000; 342(05): 314-319.

17. Velisek L, Moshe SL, Xu SG, Cammer W. Reduced Susceptibility to Seizures in Carbonic Anhydrase-Ii Deficient Mutant Mice. Epilepsy Research. 1993; 14(02): 115-121.

18. Velisek L. Veliskova J. Anticonvulsant action of carbonic anhydrase inhibition. Sbornik Lekarsky 1994; 95(03): 161-171.