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Anticonvulsant Activity: An Overview

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ABSTRACT:

Epilepsy characterized by recurrent and unprovoked seizures is a brain disorder in which clusters of nerve cells, or neurons, in the brain signal abnormally. Neurons normally generate electrochemical impulses that act on other neurons, glands, and muscles to produce human thoughts, feelings, and actions. In epilepsy, the normal pattern of neuronal activity becomes disturbed, causing stranger sensations, emotions, and behavior, or convulsions (seizures with motor manifestations), muscle spasm, and loss of consciousness. In present article we reported mechanisms of action of antiepileptic drugs, anticonvulsant agents, side effects of antiepileptic drugs, interactions of drugs associated with antiepileptic agents, naturally-occurring compounds antiepileptic compounds.

Keywords Anticonvulsant agents, mechanism of antiepileptic agents, naturally-occurring compounds antiepileptic compounds

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Introduction:

Traditional medicinal practices have remained as a component of health care system of many societies in spite of the availability of well established alternatives. Epilepsy is a condition, which causes seizures to occur. It is one of the most common chronic diseases affecting human beings. According to several publications this can amount to 70% of the people with epilepsies, with a high prevalence of about 0.8% in children below the age of seven years[1, 2, 3].

Epilepsy is a major neurological disorder and up to 5% of the world population develops epilepsy in their lifetime[4]. The current therapy of epilepsy with modern antiepileptic drugs is associated with side effects, dose-related and chronic toxicity, as well as teratogenic effects, and approximately 30% of the patients continue to have seizures with current antiepileptic drugs therapy[5, 6]. Traditional systems of medicine are popular in developing countries and up to 80% of the population relies on traditional medicines or folk remedies for their primary health care need[7].

Epilepsy is a condition in which a person has recurrent seizures. The mainstay of treatment for epilepsy remains symptomatic despite the rapid expansion in knowledge of its neurological disabilities. Therapeutic options, both medical, surgical and non medical have been markedly improved over the past decades, resulting in better condition, activities of daily living, and quality of life for epileptic patients. Various pharmacologic and surgical options are available, including different formulations. There are number of drugs available for treatment of epilepsy in modern therapy. But the major disadvantages being faced are their chronic side effects. Herbal drugs are acting at target side having same mechanism of action as that of synthetic drugs. With the introduction of allopathic drugs, the use of crude drugs from medicinal plants is on

the decline and subsequently this traditional knowledge may be lost in the near future. Novel antiepileptic drugs are better tolerated by epileptic patients and practically are devoid of important pharmacokinetic drug interactions[8].

Mechanisms of action of antiepileptic drugs[9]

Three major mechanisms of action are recognised: modulation of voltage-gated ion channels; enhancement of gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; and attenuation of glutamate-mediated excitatory neurotransmission.

Voltage-gated ion channels[9]:

Ion channels regulate the flow of positively and negatively charged ions across neuronal cell membranes and ultimately control the intrinsic excitability of the nervous system. Voltage-gated sodium channels are responsible for depolarisation of the nerve cell membrane and conduction of action potentials across the surface of neuronal cells. At nerve terminals, voltage-gated calcium channels are recruited by sodium channel dependent depolarisation, leading to calcium entry, neurotransmitter release and chemical signaling across the synapse. Calcium channels are distributed, on a cellular and anatomical basis, according to physiologically defined sub-types.

Inhibitory neurotransmission[9]:

GABA is the predominant inhibitory neurotransmitter in the mammalian central nervous system and is released at up to 40% of all synapses in the brain. GABA is synthesized from glutamate by the action of the enzyme glutamic acid decarboxylase. Following release from GABAergic nerve terminals, it acts on the post-synaptic GABAA receptor, a ligand-gated ion channel comprising five independent protein subunits arranged around a central chloride ion pore. Nineteen GABAA receptor subunits have been identified to date (α1−6, β1−3, γ1−3, δ, ε, θ, π, ρ1−2), any five of which could in theory form a functional channel (in reality only a handful of combinations are observed), with subunit composition conferring physiology and pharmacology. The GABAA receptor responds to GABA binding by increasing chloride ion conductance resulting in fast neuronal hyperpolarisation or inhibition. In contrast, the G-protein-coupled GABAB receptor mediates slow hyperpolarisation of the post-synaptic membrane and is also found pre-synaptically where it acts as an auto-receptor, with activation limiting further GABA release. GABA is removed from the synaptic cleft into localised nerve terminals and glial cells by a family of transport proteins, denoted GAT-1, GAT-2, GAT-3, and BGT-1. Thereafter, GABA is either recycled to the readily releasable neurotransmitter pool or inactivated by the mitochondrial enzyme GABA-transaminase.

Excitatory neurotransmission[9]:

Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Following release from glutamatergic nerve terminals, it exerts its effects on three specific subtypes of ionotropic receptor in the postsynaptic membrane, designated according to their agonist specificities − AMPA, kainate and NMDA. These receptors respond to glutamate binding by increasing cation conductance resulting in neuronal depolarisation or excitation. The AMPA and kainate receptor subtypes are permeable to sodium ions and are involved in fast excitatory synaptic transmission. In contrast, the NMDA receptor is permeable to both sodium and calcium ions and, owing to a voltage-dependent blockade by magnesium ions at resting membrane potential, is only activated during periods of prolonged depolarisation, as might be expected during epileptiform discharges. Metabotropic glutamate receptors perform a similar function to GABAB receptors; they are G-protein coupled and act predominantly as auto-receptors on glutamatergic terminals, limiting glutamate release. Glutamate is removed from the synapse into nerve terminals and glial cells by a family of specific sodium-dependent transport proteins (EAAT1−EAAT5) and is inactivated by the enzymes glutamine synthetase (glial cells only) and glutamate dehydrogenase.

Anticonvulsant agents[10]:

In the following list, the dates in parentheses are the earliest approved use of the drug.

1. Aldehydes: Paraldehyde. One of the earliest anticonvulsants. Still used to treat status epilepticus, particularly where there are no resuscitation facilities.
2. Aromatic allylic alcohols: Stiripentol. Indicated for the treatment of severe myoclonic epilepsy in infancy (SMEI).
3. Barbiturates: Barbiturates are drugs that act as central nervous system (CNS) depressants, and by virtue of this they produce a wide spectrum of effects, from mild sedation to anesthesia. The following are classified as anticonvulsants: Phenobarbital, Methylphenobarbital, Metharbital, Barbexaclone.
4. Benzodiazepines: Clobazam, Clonazepam, Clorazepate, Diazepam, Midazolam, Lorazepam, Nitrazepam, temazepam, and especially nimetazepam are powerful anticonvulsant agents.
5. Bromides: Potassium bromide (1857). The earliest effective treatment for epilepsy.
6. Carbamates: Felbamate.
7. Carboxamides: Carbamazepine.
8. Fatty acids: The following are fatty-acids: The valproates
9. GABA analogs: Gabapentin, Pregabalin.
10. Hydantoins: Ethotoin, Phenytoin, Mephenytoin
11. Oxazolidinediones: Paramethadione, Trimethadione, Ethadione, Propionates, Beclamide,
12. Pyrimidinediones: Primidone.
13. Pyrrolidines: Brivaracetam, Levetiracetam, Seletracetam.
14. Succinimides: Ethosuximide, Phensuximide, Mesuximide,
15. Sulfonamides: Acetazolamide, Sultiame, Methazolamide, Zonisamide.

16. Triazines: Lamotrigine.
17. Ureas: Pheneturide, Phenacemide.
18. Valproylamides (amide derivatives of valproate): Valpromide, Valnoctamide

New Antiepileptic Drugs[11]:

Therapy with standard antiepileptic drugs (AEDs) has been effective in controlling seizures (the clinical manifestation of abnormal neuronal hyperactivity) in approximately 75% of those children and adults[12].

Felbamate Felbamate (Felbatol) was introduced in the United States in 1993 as adjunctive or monotherapy to treat partial seizures with or without secondary generalization in adults[13]. It is also used in children to treat Lennox-Gastaut syndrome-a severe form of childhood epilepsy characterized by several types of seizures, developmental delay, and behavior disturbances. Based on anecdotal reports, felmabate may also be effective in the treatment of absence seizures, juvenile myoclonic (brief body jerk) epilepsy, Landau-Kleffner syndrome (a rare form of childhood epilepsy, which results in severe language disorder), and juvenile spasm. The most common adverse effects of felbamate are anorexia, weight loss, and insomnia[11,14].

Gabapentin Since gabapentin (Neurontin) was released in 1994, it has become popular as a new AED because of its ability to be titrated quickly, mild adverse effect profile, lack of enzyme-altering properties, and general lack of significant drug-drug interactions. It has demonstrated efficacy against partial seizures in both adults and children[11,12].

Lamotrigine Released in 1995, lamotrigine (Lamictal) is approved for the add-on treatment of partial seizures. It has proved effective in treating patients with primary generalized seizures, including tonic-clonic (sudden sharp contraction of muscle), absence, myoclonic, and atonic (loss of tone and unconsciousness), and in patients with Lennox-Gastaut syndrome or seizures secondary to brain injury[11,13].

Topiramate Topimate (Topamax) was approved in 1997 for use as an adjunctive treatment of partial seizures that affect only one cerebral hemisphere (in part or totally) in adults. Topimate is considered a broad-spectrum AED because it is also effective in the treatment of juvenile myoclonic epilepsy, other primary generalized epilepsies, and Lennox-Gastaut syndrome. Topimate can also be used as monotherapy for partial seizures[11,14].

Tiagabine Tiagabine (Gabitril) was approved in October 1997 and is indicated as an adjunctive therapy in partial and secondary generalized seizures (associated with neurological abnormal and delayed psychomotor development and indicative of diffuse cerebral pathology). Trials have proved its efficacy as monotherapy[11,12].

Vigabatrin Vigabatrin (Sabril) is available in most countries but is still not approved in the United States. Studies of vigabatrin in adults have clearly demonstrated its efficacy against partial seizures, with little or no efficacy against other seizure types. In children, the efficacy of this AED does not seem to be limited to partial seizures. In fact, vigabatrin has emerged as a potential first-choice AED against infantile spasms (sudden flexion of the trunk, neck, and limbs, followed by more gradual relaxation) [11,15].

Oxcarbazepine Oxcarbazepine (Trileptal) has been approved by the FDA as a monotherapy for the treatment of partial seizures in adults and children as young as 4 years old. Oxcarbazepine is similar to carbamazepine in terms of efficacy and indications, and it is generally viewed as an alternative to carbamazepine, especially in patients who cannot tolerate it. In addition, oxcarbazepine is not effective against absence seizures[11,16]. Side effects associated with oxcarbazepine include nausea, headache, dizziness, diarrhea, vomiting, upper respiratory tract infection, constipation, dyspepsia, ataxia, and nervousness.

General side effects of antiepileptic drugs Diarrhea, Vomiting, Upper respiratory tract infection, Constipation, Dyspepsia, Ataxia, Nervousness, Allergic skin reaction, Nausea, Headache, Dizziness, Aplastic anemia, Hepatic failure.

The cognitive side effects[17] of carbamazepine (Equetro, Tegretol), phenytoin (Dilantin) and valproate sodium (Depacon) are comparable and associated with modest psychomotor slowing accompanied by decreased attention and memory. Neuropsychological side effects generally emerge according to a dosedependent relationship; however, both quality of life and memory may be affected, even when serum blood concentrations are within standard therapeutic ranges. In children, AED effects are seen in decreased performance on the Continuous Performance Test (CPT) or memory. In addition, some children are at heightened risk for developing disproportionate cognitive side effects with carbamazepine. Treatment with carbamazepine has also been associated with electroencephalogram slowing in the alpha range. How these short-term effects translate into academic achievement has not been adequately established. However, there appears to be some relationship between the magnitude of EEG slowing and subsequent decline on selected Wechsler Intelligence Scale for Children-Revised (WISC-R) subtests tested after one year of therapy.

Interactions of drugs associated with antiepileptic agents[18]:

Epilepsy is a chronic disease that may require long-term antiepileptic drug therapy. The efficacy of single-agent antiepileptic drug therapy for the treatment of epilepsy is well established[19]. For those patients with epilepsy who do not respond to single-agent therapy, treatment with multiple antiepileptic drugs is necessary. A recent survey indicated that 28% of patients with epilepsy were prescribed polytherapy[20]. Polytherapy is frequently necessary for the treatment of co morbidities in patients with epilepsy. Antiepileptic drugs are known to interact with cardiovascular agents including

anticoagulants, beta-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins"). Moreover, antiepileptic drugs are commonly prescribed to treat a variety of non epileptic conditions including migraine headache, chronic neuropathic pain, mood disorders, and schizophrenia. In 2003, 45% of antiepileptic drugs prescribed by neurologists were for conditions other than epilepsy[21], while 96% of antiepileptic drugs prescribed by psychiatrists were for non epileptic use; predominantly bipolar disorder and schizophrenia.

The teratogenicity[22] of anticonvulsant drugs shows that a distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of anticonvulsant drugs during pregnancy, rather than with epilepsy itself. Anticonvulsant drugs taken by pregnant women to prevent seizures are among the most common causes of potential harm to the fetus. In the 1970s and 1980s, the anticonvulsant drugs used most frequently to prevent seizures-phenobarbital, phenytoin, and carbamazepine were found to cause major malformations, microcephaly, growth retardation, and distinctive minor abnormalities of the face and fingers in infants exposed to them during pregnancy.

Moreover, epilepsy is very often associated with CNS psychiatric disorders[23]. Furthermore, the discovery of Ziprasidone led the exploration of oxindole. Ziprasidone is a novel effective atypical antipsychotic agent having an oxindole scaffold and has been recently approved by Food and Drug Administration (FDA) for the treatment of schizophrenia[23]. As with other atypical antipsychotics, the precise mechanism of action of the new drug is not know. Ziprasidone was, however, known to be a potent serotonin and dopamine antagonist[23].

Metabolic acidosis in a pediatric patient receiving topiramate[24] Topiramate is an anticonvulsant that is labeled for the management of several seizure types in children>2 years of age. With the exception of cognitive dysfunction, nephrolithiasis, weight loss, andparesthesia, adverse effects in children are similar to other those noted with other anticonvulsants. 33-month old child with complex partial seizures and secondary generalization who received topiramate 45 mg orally twice daily (6.2 mg/kg/d) for approximately 4 weeks before admission. He developed asymptomatic metabolic acidosis that was evidenced by a decrease in HCO^{3-}, which was unresponsive to treatment with sodium bicarbonate. The child was weaned off topiramate and the metabolic acidosis resolved 48 hours after its discontinuation.

Discovery of lesser neurotoxic and effective anticonvulsant agents active in four animal models of seizure[25]

A series of disubstituted aryl semicarbazones were prepared and characterized using spectral data. The compounds were screened for anticonvulsant properties in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), strychnine (scSTY) and picrotoxin (scPIC) seizure threshold tests in mice. Neurotoxicity was determined using the rotorod test in mice. The compounds were also studied for behavioral despair and depression using actophotometer and porsolt's swim pool test respectively. All of the compounds showed anti-MES activity. In particular, seven compounds emerged as wide-spectrum active anticonvulsants being active in all the four animal models of seizure. The ED50 of the most potent compound was 17.74 ± 1.66 mg/kg. These compounds were also found to be less neurotoxic (TD50 > 300 mg/kg) compared to the standard anticonvulsant agents.

Investigation of antiepileptic drugs from naturally-occurring compounds:

Current available anticonvulsant drugs are able to efficiently control epileptic seizures in about 50% of the patients; another 25% may show improvement whereas the remainder does not benefit significantly[26]. Furthermore, undesirable side effects of the drugs used clinically often render treatment difficult so that a demand for new types of anticonvulsants exists. One of the approaches to search for new antiepileptic drugs is the investigation of naturally-occurring compounds, which may belong to new structural classes.

Anticonvulsant activity of the leaves of *Glycyrrhiza glabra* var. *glandulifera*[28] The anticonvulsant activity of the leaves' ethanol extract and dichloromethane, *n*-Hexane, and methanol, fractions were evaluated intraperitoneally in mice using maximal electroshock (MES) and pentylenetetrazol (PTZ) seizure tests. Acute toxicity of the extract and the fractions were also assessed. Phytochemical screening of the extract and the fractions for their active constituents was also carried out by thin layer chromatography and various chemical reagents. The extract and the fractions showed anticonvulsant effect in PTZ test.

Anti epileptic activity of *Morinda citrifolia* linn fruit extract[27]
Estimation of duration of epileptic seizures: The animals were divided into four groups (n=6) and group I animals served as control receiving 1 mL of 5% CMC p.o, group II served as drug control receiving phenytoin 20 mg/kg, p.o and group III and IV animals were administered with the *M.citrifolia* fruit extract at doses of 200 and 400 mg/kg, p.o for 15 days respectively. On the 15th day, seizures were induced to all the groups of animals using electro convulso meter. A 60 Hz alternating current of 150 milliamps intensity elicited maximal electro shock (MES) seizures for 0.2 second. A drop of electrolyte solution (0.9% NaCl) with lignocaine was applied to the corneal electrodes prior to application to the rats. This increases the contact and reduces the incidence of fatalities.

Estimation of biogenic amines

The animals were divided into five groups (n=6) and Group I animals served as control for reference standards, Group II animals served as negative control receiving 1 mL of 5% CMC p.o, group III served as drug control receiving phenytoin 20

mg/kg p.o, group IV animals were administered with the *M.citrifolia* fruit extract at a dose of 200 mg/kg p.o and group V animals received *M.citrifolia* fruit extract at a dose of 400 mg/kg p.o for 15 days.

Anticonvulsant activity of *Carissa carandas* linn.[3] *Electrically-induced seizures:* In the electrically-induced seizure experiment, the maximal electroshock (MES) method. In brief, tonic convulsions of the hind extremities of the mice were induced by passing alternating electrical current of 50 Hz and 150 mA for 0.2 sec through corneal electrodes. The number of animals protected from hind limb tonic extension seizure (HLTE) and the time spent in this position were determined for each dose group.

Chemically-induced seizures: Seizures were induced in mice with standard convulsing agents pentylenetetrazole (PTZ), picrotoxin (PC), bicuculline (BC) or N methyl-dl-aspartic acid (NMDLA) and the animals were observed for 30 min for tonic convulsion episode. Hind limb extension was taken as tonic convulsion. The onset of tonic convulsion and the number of animals convulsing or not convulsing within the observation period were noted. The ability of the plant extract to prevent or delay the onset of the hind limb extension exhibited by the animals was taken as an indication of anticonvulsant activity.

Anticonvulsant activity of *Tacazzea apiculata* oliv. (periplocaceae)[29] The methanol extract of *Tacazzea apiculata* root-bark was subjected to successive fractionation with chloroform and n-butanol. The maximal electroshock test (MEST) in chicks and pentylenetetrazole-induced seizure were carried out on n-butanol fraction (TBF) to evaluate its anticonvulsant effects in chicks and mice respectively. Diazepam-induced sleep in mice was used to evaluate the sleep-potentiating activity of TBF. The fraction protected 80% of the chicks against MEST at doses of 10 and 20mg.kg-1. The fraction did not protect the mice against pentylenetetrazole-induced seizure.

Anticonvulsant activity of ethanolic extract of *Cynodon dactylon*[30] Anticonvulsant activity was studied against maximal electroshock (MES) and Pentylenetetrazol (PTZ) induced convulsions in mice. The extract suppressed hind limb tonic extensions (HLTE) induced by MES and also exhibited protector effect in PTZ-induced seizures. In conclusion the ethanolic extract of Cynodon dactylon has anticonvulsant effect in the both models, suggesting their possible depressant action in the central nervous system.

Anticonvulsant activity of *Vitex-negundo*[31] Maximal electroshock seizures (MES) in albino rats and pentylenetetarazole (PTZ) induced seizures in albino mice were used to study anticonvulsant activity of *Vitex-negundo* leaf extract. The ethanolic leaf extract of *Vitex-negundo* was administered orally in graded doses (250, 500 and 1000 mg/kg p.o) in both the experimental models and the effects were compared with diphenylhydantoin in MES method and valporic acid in PTZ induced seizures method as standard control respectively. The *Vitex negundo* in the doses (250, 500 and 1000 mg/kg, p.o) did not show protection against MES to any significant extent but significant post-ictal depression was observed in the dose of 1000 mg/kg body weight in comparison to control. However, sub-protective dose of test drug (100 mg/ kg, p.o) potentiated the anticonvulsant action of diphenylhydantoin. The test drug in the dose (1000 mg/kg, po) showed 50% protection in clonic seizures and 24-hour mortality against PTZ induced seizures.

Conclusion:

New AEDs have broadened the therapeutic options in treating patients with refractory epilepsy and those who cannot tolerate conventional therapy. Although these drugs are promising, further clinical experience will be necessary to validate the usefulness of these agents. Our article will helpful for researcher to find out newer antiepileptic drugs with lesser side effects.

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