A REVIEW ON ANTIEPILEPTIC AGENTS, CURRENT RESEARCH AND FUTURE PROSPECTUS ON CONVENTIONAL AND TRADITIONAL DRUGS

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ABSTRACT

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. The principle of seizure (Epilepsy) management should be individualized and the selection of treatments should aim to control symptoms as well as to prevent other complications. 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.

Keywords: Epilepsy, modern therapy, synthetic drugs, medicinal plants.

INTRODUCTION

The last ten years of the 20th century is called in neuroscience “decade of the brain”. Epilepsy usually begins in childhood, potentially impeding education, employment, social relationships and development of a sense of self-worth.[1] Epilepsy is among the disorders that are strongly associated with significant psychological and social consequences for everyday living.[2] There is no doubt that epilepsy belongs to the most encountered neurological conditions since the disease affects approximately 1% of the population. According to several publications this can estimate to 70% of the people with epilepsies, with a high prevalence of about 0.8% in children below the age of seven years[3]. Around 75-80% of epileptic patients may be provided with adequate seizure control with the help of conventional antiepileptic drugs. Carbamazepine, ethosuximide, phenobarbital, phenytoin, and valproate are the most frequently used conventional antiepileptics. The therapeutic failure in 20-25% of patients has stimulated intensive research on novel antiepileptic drugs and so far most of them have been developed and licensed mainly as add-on treatment in patients poorly responding to conventional therapy. These are felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, and zonisamide[4]. This period has brought many new antiepileptic drugs (AEDs) to the practising physician. Long-term antiepileptic drug therapy is often necessary for the majority of patients diagnosed with epilepsy. For those patients who do not respond to single-agent therapy, treatment with multiple antiepileptic agents is required. Antiepileptic drugs are well-known for their drug interactions; not only between each other, but also with other pharmacologic agents. These observations have led to a shift in focus to the use of herbal remedies in the management of epileptic seizures. In conventional drug it is necessary to administration of antiepileptic agents necessitates vigilant monitoring by physicians of possible drug interactions and their resulting clinical consequences. However, a thorough understanding by the physician of antiepileptic drug interactions is critical in anticipating, and thus preventing, potential adverse outcomes associated with antiepileptic drug interactions. For example, physicians must be cognizant that drug *discontinuation* may have an equally serious impact on the efficacy or toxicity of remaining drug therapy as does the *addition* of an antiepileptic drug to existing drug therapy. The development of these drugs was under the current epilepsy theory (balance disturbances between inhibitory and excitatory neurotransmitters in the brain). Mechanism of action of the new AEDs is due to increase of the GABA-system activity and / or reaction with ion-channels events in neurons. Epilepsy is one of the most common neurological disorders with reported prevalence of 6-8/100,000 incidence of 30-50/100,000 per year and cumulative incidence of 3%. It requires prolonged and sometimes life-long drug therapy[6.] Available anti-epileptic drugs are categorized into three major groups: Conventional and traditional, conventional anti-epileptic drugs approved before 1990; new antiepileptic drugs approved after 1990 and unconventional antiepileptic drugs that are not normally used to treat seizures or may have serious side effects[7]. Although the new antiepileptic drugs (AEDs) are already in use in worldwide. Selecting the best drug for a particular patient and for specific seizure type can be confusing for the physician sometimes and patients may even solicit these medications from abroad. Long-term antiepileptic drug therapy is often necessary for the majority of patients diagnosed with epilepsy. For those patients who do not respond to single-agent therapy, treatment with multiple antiepileptic agents is required. Despite the advent of new antiepileptic drugs (AEDs), more than 30% of epilepsy patients remain poorly controlled with current AEDs. For these patients, combined administration of AEDs or the application of

novel AEDs are the most appropriate therapeutic options when surgical treatment cannot be offered. Second-generation and more recently developed AEDs tend to offer new mechanisms of action and more favourable safety profiles than the first-generation AEDs. Traditional medicinal practices have remained as a component of health care system of many societies in spite of the availability of well-established alternatives, Plants have been used by mankind for their relieving and therapeutic abilities and still we rely on their healing properties. [8] Plants having active constituent have a direct pharmacological action on our body including various organs like brain. The Indian system of medicine "Ayurveda" classified the plants affecting the brain and other major organs. Antiepileptic drugs are well-known for their drug interactions; not only between each other, but also with other pharmacologic agents. Many therapeutic agents undergo metabolism prior to elimination from the body. The major site of drug metabolism is the liver and the predominant enzyme system for drug metabolism is the cytochrome P450 family located in the endoplasmic reticulum of hepatocytes. Cytochrome P450 enzymes reduce or alter the pharmacologic activity of many drugs and facilitate their elimination.[9] The activity of cytochrome P450 enzymes can be increased or decreased by endogenous compounds or by the presence of some drugs. The consequence of altered enzyme activity can be an increase or decrease in the concentrations of drugs metabolized by these enzymes (ie, substrate drug). The characteristics of alteration in enzyme activity of the cytochrome P450 family have been the focus of research for over twenty years. A review of the pharmacology, pharmacokinetics, indications and side effects of these new anti-epileptic drugs with the current understanding of their various clinical profiles is therefore required to provide their judicious use locally. Complementary and alternative medicine (CAM) is recognized to be commonly used by patients, yet there have been few studies regarding the scope of CAM and patients with epilepsy. The aim of this work was a short overview of the current literature and results for antiepileptic agents.

Antiepileptic Drugs (Conventional):

Gabapentin (NEURONTIN) is a structural analogue of gamma- aminobutyric acid (GABA) which does not interact with either $GABA_A$ or $GABA_B$ receptors, convert to GABA or GABA agonist nor does it inhibit GABA up-take or degeneration[10]. Although its mechanism of action is unknown, it may increase the total central nervous system level of GABA[11]. It has been shown to be effective in complex partial seizures with or without secondary generalization and generalized tonic-clonic seizures.

Lamotrigine (LAMICTAL) acts by inhibiting the release of excitatory amino acids such as glutamate through the modulation of sodium and calcium channels[12]. And lamotrigine is effective as an add-on or monotherapy for patients with partial seizures with or without secondary generalization, and in addition, in the treatment of absence, myoclonic seizures, and other seizure types associated with Lennox-Gastaut syndrome[13].

Vigabatrin (SABRIL) is a synthetic GABA derivative which causes irreversible inhibition of GABA transaminase thereby increasing the pool of the inhibitory neurotransmitter[14].

Topiramate (TOPAMAX) is a sulfamate-substituted monosacharide with carbonic anhydrase inhibitory properties. The mechanism of action as an antiepileptic drug is related to inhibition of $GABA_A$ receptor mediated activities and its direct modulating effect is independent of carbonic anhydrase inhibition[15].

Tiagabine (GABATRIL) exhibits its epileptic activity through selective GABA re-uptake inhibition[16]. It increases the serum levels of Phenytoin and Valproic acid and is effective as an add-on therapy in patients with partial seizures with or without secondary generalization[17].

Levetiracetam (KEPPRA) has a novel binding site (90K da binding site) which is the synaptic vesicle protein (SV2A) present in synaptic vesicles and some neuroendocrine cells[18]. Its mechanism of action is distinct from that of other anti-epileptic drugs. Levetriacetam is effective in patients with partial seizures with or without secondary generalization and the main side effects include behavioural disturbances which may necessitate discontinuation.[19]

Zonisamide (ZONEGRAN) exerts its antiepileptic activity by blocking voltage-sensitive sodium and voltage-dependent calcium channels, enhances GABA release, blocks the potassium glutamate response and reduces glutamate-mediated synaptic excitation[20]. Zonisamide is effective as an add-on therapy in generalized seizures and partial seizures with or without secondary generalization; the main side effects include somnolence, dizziness and nephrolithiasis.[21]

Oxcarbazepine (TRILEPTAL) and its active metabolite (10 monohydroxy epoxide derivative) block voltage dependent sodium and voltage-activated calcium channels.[22] Oxcarbazepine is similar to carbamazepine in its spectrum of anti-convulsant activity. It is currently recommended as either a first line monotherapy or an add-on therapy for partial seizures with or without secondary generalization with the major side effects of hyponatremia and hypersensitivity reaction.[23]

Felbamate (FELBATOL) is thought to act by the inhibition of the excitatory NMDA receptors although the exact mechanism of action remains unknown.[24] The drug is effective in the treatment of refractory partial seizure and Lennox-Gastaut syndrome since its introduction in 1993.

The new antiepileptic drugs in women, pregnancy and lactation Some of the new AEDs particularly Gabapentin, Topiramate, Vigabatrin and Levetriacetam have minimal protein binding properties and do not cause hepatic enzyme induction, and as such do not interact with oral contraceptive pills.

New antiepileptic drugs:

Newer AEDs such as Pregabalin and Retigabine have been shown to be effective against partial seizures and are currently undergoing further clinical trials.[25]

Fosephenytoin, a Phenytoin is useful particularly in the treatment of status epilepticus. The newer formulation of intravenous Valproate has been approved for use in patients for whom oral administration is temporarily not feasible. The search for antiepileptic agents with more selective activity and lower toxicity continues to be an area of intensive investigation in neuroscience. There are many chemical compounds have been tested as antiepileptic agents. The drugs in most advanced development (including clinical studies) are: atipamezole, BIA-2-093, fluorofelbamate, NPS 1776, pregabalin, retigabine, safinamide, stiripentol, talampanel, ucb 34714 and valrocemide. Part of them is chemical derivative from marketed AEDs, the other representing new structural classes of compounds, for which the precise mechanism of action in epilepsy is still unknown. First clinical trials with these compounds are very promising.[27] The development of new AEDs has expanded therapy options and offered advantages to the patient. Although clinical trials show that new AEDs are not efficacious when compare to the classical drugs.

Traditional antiepileptic drugs:

Recently, the interest in the use of herbal products has grown dramatically in the western world as well as in developed countries.[28] It is now becoming exceedingly apparent that available psychotherapeutics does not properly meet therapeutic demands of a vast majority of patients with mental health problems, and that herbal remedies remain to be the ultimate therapeutic hope for many such patients in the western world and elsewhere.[29] Useful herbs for the treatment of epilepsy (Generalised epilepsy) Abies mariana, Acorus calamus, Acorus gramineus, aethusa cynapium, Anacyclus pyrethrum, Anamirta cocculus, Anthemis cotula, Artemisia nilgirica, Artemisia vulgaris, asparagus recemosus, bacopa monnieri, ballota nigra, benincasa hispida, betula utilis, blighia sapida, brassica nigra, calamus rotang, caltha palustris, cassia occidentalis, celastrus paniculatus, cicuta virosa, cinnamomum camphora, citrus grandis, cleome gynansra, colebrookea oppositfolia, colius amboinicus, cynodon dactylon, cyperus rotundus, datura metel, desmodium triflorum, discorea dregeana,elaeocarpus sphaericus, entada pursaetha, gmelina arborea, humulus lupulus, indigofera tinctoria, limonia acidissima , martynia annua, moringa oleifera, myrtus communis, nardostachys jatamansi, paeonia emodi, picrorhiza kurroa, paeonia officinalis, ruta graveolens, salix tetrasperma, sambucus nigra, sapindus mukorossi, sebania grandiflora, streblus asper, strychnous nox-vomica, taxus baccata, valeriana officinalis, vibumum prunifolium, viola tricolor, xanthium strumarium, zanthoxylum alatum.

Brunsvigia grandiflora (F- Amaryllidaceae), Acokanthera olongifolia (F- Apocyanaceae), Bulbine Frutescens (F- asphodelaceae), Rhus chirindensis (F- Anacardiaceae),Cussonia Spicata (F- Araliaceae), Gasteria Croucheh (F- Asphodelacea), Combreturn bracteosum (F- Combretaceae), Antedesma Venonum (F- Euphorbiaceae), Abrus Precatorius (F-Leguminosae), abrus Schimperiana (Leguminosae), Adhatoda engleriana landau (F- Acanthaceae), Aloe (F-Liliaceae), Canthium hispidum benth (F-Rubiaceae), Casia Fistula (F-Leguminaceae), Curcuma longa (F- Zingiberaceae), Ocimum Suave willd (F- Labiateae).

Future prospectus for diagnosis and treatment of epilepsy:

It is quite pertinent that commonly available synthetic anticonvulsants do not adequately meet patient treatment demands.

1) Ketogenic diet- a highly fat, low carbohydrate diet developed with the advent of effective anticonvulsants. The mechanism of action is unknown. It is used mainly in the treatment of children with severe, medically intractable epilepsies.[30]
2) Electrical stimulation- A currently approved device is vagus nerve stimulation. Investigational devices include the responsive neurostimulation system and deep brain stimulation.[31]
3) Vagus nerve stimulation- The device stimulates the vagus nerve at pre-set intervals and intensities of current. Efficacy has been tested in patients with localization-related epilepsies.[32]
4) Responsive neurostimulator system (RNS)-It consists of a computerised electrical device implanted in the skull with electrodes implanted in presumed epileptic foci within the brain. The brain electrodes send EEG signal to the device which contains seizure detection software. When certain seizure criteria are met, the device delivers a small electrical charge to other electrodes near the epileptic focus and disrupt the seizure.[33]
5) Deep brain stimulation-Consists of computerised electrical device implanted in the chest in a manner similar to the VNS.[34]
6) Non invasive therapy- Use of Gamma knife device is used in neurosurgery are currently being investigated as alternatives to traditional open surgery in patients who would otherwise qualify for anterior emporal lobectomy.[35,36]
7) Avoidance therapy- Avoiding therapy consists of minimising or eliminating triggers in patients whose seizures are particularly susceptible to seizure participants.[37]

There is a strong correlation between the ethanopharmacological usage with that of scientifically proven claims which justify and hence supports the traditional therapy not only India but also other countries.

CONCLUSION

Seizure activity leads to neuronal cell loss and, as it has been already mentioned, neurodegeneration may affect the protective activity of some antiepileptic drugs. New antiepileptic drugs are now available for the treatment of various forms of seizures and the epilepsy syndromes. Lamotrigine and Topiramate are effective as initial monotherapy for generalized seizures, and Topiramate, Lamotrigine, Oxcarbazepine and Gababentin for partial onset seizures. Zonisamide is effective as an add-on therapy for patients with partial seizures and may additionally act as a free radical scavenger thereby provide additional protection of neurons. Novel antiepileptic drugs

enhancing GABA-mediated events usually possess a better pharmacological profile in experimental epilepsy models than conventional antiepileptic drugs and generally, their pharmacokinetics in humans is more predictable. Drug interactions are rather rare. In open label trials, good results have been reported – for instance, at least 50% reduction in seizure frequency was observed in 50% of patients taking vigabatrin, 20-30% - gabapentin and 26-30% - tiagabine (partial seizures). In cases of drug resistant epilepsies, double-blind placebo controlled trials indicate that maximum 10% of patients benefit from add-on therapy with these antiepileptics. The difficulty encountered in treating patients with various seizure types and choosing the right AED on an individual basis particularly when new agents are being marked suggests that further research is needed in epileptogenesis, how to stop seizures, and possibly cure the underlying lesional pathology.

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